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KINETICS AND MECHANISM OF AROMATIC HALOGENATION: BROMINATION OF ANISOLE WITH BROMINE IN GLACIAL AND AQUEOUS ACETIC ACID AND CARBON TETRACHLORIDE

By Lourdu M. Yeddanapalli and N. S. Gnanapragasam

In glacial acetic acid, the overall kinetic order of the bromination of anisole decreases from 3 at 0.1*M* to 2.3 at 0.001*M*, and the activation energy increases from 4.04 kcal./mole at 0.04 *M* to 9.92 kcal./mole at 0.001*M*. In aqueous acetic acid, the reaction is of second order and extremely fast ; in 75% aqueous acetic acid, the rate is 1210 times that in glacial acetic acid.

In carbon tetrachloride the anisole—bromine reaction is autocatalytic and of third order. The autocatalysis is caused by the hydrogen bromide produced in the initial stages of the reaction. The effect of varying amounts of pyridine on the rate of bromination of anisole has also been investigated.

A spectrophotometric study indicates that intermolecular complexes between iodine and anisole, iodine and benzene, and bromine and benzene are formed in carbon tetrachloride, but not in glacial acetic acid. In keeping with this finding, reaction mechanisms are proposed for the bromination of anisole in the two solvents.

In continuation of our work on the bromination of phenol by bromine and iodine bromide in glacial acetic acid and in carbon tetrachloride (*J. Chem. Soc.*, 1956, 4934), the kinetics of bromination of the less reactive anisole has now been investigated. The bromination of anisole by bromine is known to yield mainly *p*-bromoanisole (Slotta and Heller, *Ber.*, 1930, **63**, 3043 ; Wohl, *Ber.*, 1919, **52**, 51). De la Mare and Vernon (*J. Chem. Soc.*, 1951, 1764) showed that *p*-bromination of anisole took place to the extent of 94% in glacial acetic acid medium. A preliminary kinetic study by Robertson *et al.* (*J. Chem. Soc.*, 1943, 276) indicated the anisole-bromine reaction in acetic acid to be of third order in the concentration range of *M*/80 to *M*/160.

The bromination of acetanilide in glacial acetic acid (cf. Robertson, *loc. cit.*) exhibited certain peculiar features. The reaction was of third order at 0.025*M*, but of second order at 0.001*M*, with a corresponding increase in activation energy from 3.3 to 11.0 kcal./mole. Increase of temperature also decreased the total order of the reaction, e.g., from 3.0 at 24° to 2.5 at 50° in the range of *M*/40 to *M*/80. It seemed of interest to find out if this dependence of the kinetic order and activation energy on concentration and temperature would hold good for the bromination of anisole in glacial acetic acid.

Bromination of aromatic compounds proceeds generally faster in aqueous than in glacial acetic acid medium (Bradfield *et al.*, *J. Chem. Soc.*, 1949, 1389 ; Keefer and Andrews, *J. Amer. Chem. Soc.*, 1956, **78**, 3637 ; Brown and Stock, *ibid.*, 1957, **79**, 1421 ; Berliner and Beckett, *ibid.*, 1957, **79**, 1425; Robertson *et al.*, *loc.cit.*). As a quantitative examination of the effect of varying amounts of water in the glacial acetic acid solvent on the rate of bromination of a particular compound has not so far been made, we have measured the rate of bromination of anisole in seven aqueous acetic acid solutions

containing from 1 to 25% of water (by volume), and attempted to correlate the relative reaction rates with the dielectric constants of the solvents.

In carbon tetrachloride, the kinetics of bromination of aromatic compounds show some special characteristics. Induction periods were reported in the bromination of mesitylene (Keefer *et al.*, *J. Amer. Chem. Soc.*, 1954, **76**, 3062) and toluene (Tsuruta *et al.*, *ibid.*, 1954, **76**, 994) in carbon tetrachloride. In the bromination of phenol in the same solvent, we have observed (*loc.cit.*) that the temperature coefficient is positive between 0° and 10°, but negative between 20° and 30°. In view of these findings, it is of interest to study the bromination of anisole in this solvent. The exact role of pyridine, which is considered to be a 'halogen carrier', has also been examined, using anisole and bromine in carbon tetrachloride.

Experimental

The procedure for the rate-measurements was similar to the one reported earlier (*loc.cit.*) excepting that 2 c.c. of bromine and anisole solutions were used for each determination instead of 5 c.c. Reproducibility is illustrated by the duplicate values of 17.74 and 17.36 for the %bromine reacting in the first 5 seconds of the reaction between anisole and bromine, 0.001*M* each, in 75% aqueous acetic acid.

The preparation of the pure anhydrous acetic acid (f. p. 16.3°) was carried out by the method of Orton and Bradfield (*J. Chem. Soc.*, 1927, 983). Aqueous acetic acid solutions were prepared by adding the purified acetic acid to calculated amounts of distilled water, taken in a volumetric flask, the composition being expressed as the number of volumes of water contained in 100 volumes of the aqueous acid. Anhydrous carbon tetrachloride was prepared by fractionation of a B.P. quality sample (b.p. 76 5-77.0°/760 mm).

Bromine was shaken with H_2SO_4 (conc.) for 4 hrs., separated from the acid layer, and then distilled from freshly heated KBr. The middle fraction boiling at 58.8° was collected and kept in sealed ampoules till use. The purification of anisole (b.p. 153°) was carried out according to Everhard and Sutton (*ibid.*, 1949, 2312). Resublimed iodine was mixed with KI, sublimed, and the sublimate was used. Pyridine was dried by refluxing with NaOH pellets for 2 hours and then fractionated. The fraction boiling at 115° at atmospheric pressure was collected for use. Hydrogen bromide was produced by adding 10 c.c. of benzene to a mixture of 8 c.c. of bromine and 1 g. of iodine at 10°.

Results in Glacial Acetic Acid

Effect of Concentration and Temperature on the Overall Kinetic Order.—Rate-measurements were made using seven different initial concentrations of anisole and bromine in glacial acetic acid in the range of 0.1−0.001*M*. The overall order, calculated from the times required for definite fractions of the reaction, was found to decrease regularly with decreasing initial concentration of the reactants: for 20% reaction the values were 3.31 at 0.10−0.04*M*, 2.85 at 0.04−0.02*M*, 2.71 at 0.02−0.01*M* and 2.69 at 0.010−0.005*M*; for 10% reaction, 2.34 at 0.005−0.002*M*, and 2.28 at 0.002−0.001*M*.

The overall order is also lowered by increase of temperature: for 20% reaction, the value is 2.66 at 30° and 2.29 at 50°, in the range of 0.010−0.005*M*.

Individual Orders.—The kinetic orders with respect to anisole and bromine were determined using the isolation method, both at low and high concentrations of the reactants. Experiments were carried out with (*i*) 0.4*M* anisole and 0.04*M* bromine, (*ii*) 0.4*M* anisole and 0.02*M* bromine, and (*iii*) 0.2*M* anisole and 0.02*M* bromine, and from the data obtained, the order with respect to anisole was found to be 1, and that for bromine, 1.7. A second set of experiments at lower concentrations: (*i*) 0.02*M* anisole and 0.002*M* bromine, (*ii*) 0.02*M* anisole and 0.001*M* bromine, and (*iii*) 0.01*M* anisole and 0.001*M* bromine gave again first order for anisole and 1.3 for bromine. It is evident therefore that the fall in the overall kinetic order from 3 3 to 2.3 with decrease in the concentrations of the reactants is due to the decrease in the order of bromine.

Activation Energy.—The rate of the reaction between anisole and bromine (both 0.04*M*) was measured at 20°, 30° and 40°, and the time values required for 20, 30 and 40% reaction at each temperature were determined graphically. From these time values, the activation energy was calculated by the following method.

For a third order reaction of the type:

$$A + 2B \rightarrow \text{products}$$

with A = B = *a*, the rate expression can be written as

$$\log k = \log 1/t + \log 1/2\,[1/(a-x)^2 - 1/a^2]$$

where *a* is the initial concentration of the reactants and *x*, the amount acted upon in time *t*. Considering a definite fraction, say 20%, of the reaction at different temperatures,

$$\log k = \log 1/t + \log c$$

where *c* is a constant. Substituting the above value of log *k* in the Arrhenius equation leads to

$$\log 1/t + \log c = -E/2.303\,RT + c.$$

The plot of log 1/t against $1/T$ (°K) will therefore give rise to a straight line, whose slope will be $-E/2.303R$. This procedure is applicable to reactions of any order and avoids the difficulty of calculating rate constants for fractional order reactions of the type encountered in the present investigation.

Using the method outlined above, the activation energies are found to be 4.04, 3.97 and 4.12 kcal./mole for 20, 30 and 40% reaction at 0.04*M*, the average value being 4.04±0.1 kcal./mole. In order to evaluate the effect of decreasing concentration of the reactants on the activation energy, the reaction was also carried out with 0.001*M* anisole and bromine in the range of 20°−40°. The activation energies corresponding to 10, 15 and 20% reaction are 10.01, 9.92 and 9.84 respectively, the average being 9.92±0 1 kcal./mole.

Results in Aqueous Acetic Acid

Overall Order of the Reaction.—The anisole—bromine reaction in 97% aqueous acetic acid (*i.e.*, glacial acetic acid containing 3%, by volume, of water) has an overall order of about 2.5 in the concentration range of $0.1-0.01M$, but only 2.1 between 0.002 and $0.001M$, showing that the second order reaction predominates at the lower concentrations.

The effect of water present in aqueous acetic acid solvent is to make the bromination a bimolecular process, as shown by the fact that the overall order at $0.01-0.005M$ for 30% reaction is 2.64 in glacial acetic acid, but only 2.05 in 85% aqueous acetic acid.

Activation Energy.—The apparent energy of activation of the bromination of anisole in 97% aqueous acetic acid in the range of $20°-40°$ increases from 4.38 ± 0.1 kcal./mole at $0.04M$ to 7.71 ± 0 25 kcal./mole at $0.001M$. This change may be attributed to the decrease in the overall order from 2.5 to 2.1, when the initial concentration changes from 0.04 to $0.001M$.

Influence of Water on the Rate of Bromination in Acetic Acid.—The rate of bromination of anisole in aqueous acetic acid solutions containing 1 to 25% of water (by volume) was studied using $0.001M$ solutions of anisole and bromine. The rate was found to increase enormously with increasing water content of the solvent, viz., in acetic acid containing 25% of water (by volume), the rate is 1210 times faster than that in glacial acetic acid, as can be seen from Table I.

TABLE I

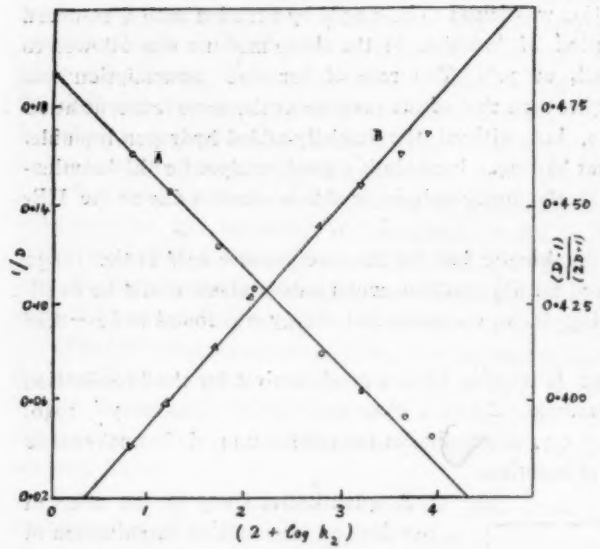
Rate of bromination of anisole in aqueous acetic acid.

Anisole $=0.001M$. Bromine $=0.001M$. Temp. $=30°$.

Water content of the medium Vol.%	Wt.%	Dielectric const. (D)	Time (sec.) for 20% reaction.	$10\times k_2$ mol^{-1} lit.sec^{-1}.	Relative k_2.	Mol. extinction at 2600Å.	4000Å.
0	0.00	6.2	7260	0.69	1.0	214.7	179.1
1	0.92	6 9	3030	1.65	2.4	229.1	174.6
3	2.88	8.2	950	5.21	7.6	267 6	174 6
5	4.83	9.6	420	11.91	17.3	288.2	175.9
10	9.23	12.8	82	60.98	88.6	309.8	175 9
15	13.85	15.9	30	166.60	242.0	327.9	174.6
20	18.54	19.3	11	454.50	660.1	368.6	173.9
25	23.13	22.5	6	833.30	1210.0	411 2	173.3

A linear relationship between the logarithm of the rate constant and $1/D$ or $(D-1)/(2D+1)$, where D is the dielectric constant of the solvent, is known to exist for bimolecular reactions between polar molecules, such as, pyridine and methyl iodide, triethylamine and ethyl iodide (Moelwyn-Hughes, 'The Kinetics of Reactions in Solution", 1947, p. 212), pyridine and benzyl bromide, and for alkaline hydrolysis of ethyl benzoate (Glasstone, Laidler and Eyring, "The Theory of Rate Processes", 1941, p. 420). A similar linear relationship holds good also in the reaction between anisole and bromine in aqueous acetic acid solutions, as shown by the plots in Fig. 1.

FIG. 1



A-Log 2nd order rate const. against $1/D$.
B, ,, ,, $(D-1)/(2D+1)$
for anisole Br reaction in aq. AcOH at 30°.

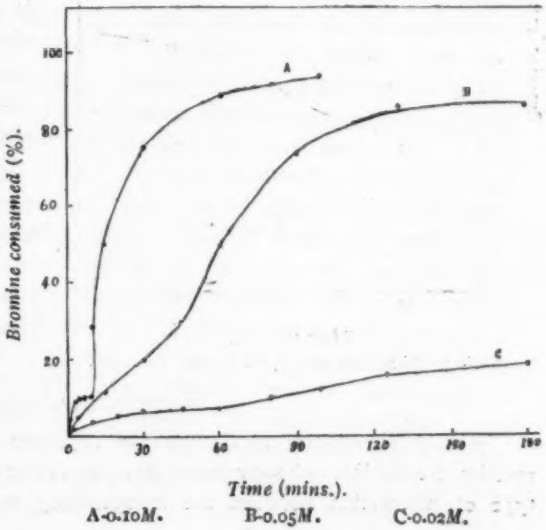
The dielectric constants of aqueous acetic acid solutions, recorded in Table I and used in Fig. 1, were calculated from the known values of acetic acid (6.20; cf. Smyth and Rogers, *J. Amer. Chem. Soc.*, 1930, **52**, 1824) and water (76.75; cf. Kortum and Bockris, "Textbook of Electrochemistry", Vol. II, 1951, p. 635) at 30°, assuming a linear variation of D with composition (wt. %), since such a relationship had been shown to hold good for the aqueous solutions of propionic acid ("International Critical Tables, Vol. VI, 1929, p.101), ethyl alcohol and acetone (Akerlof, *J. Amer. Chem. Soc.*, 1932, **54**, 4125).

Results in Carbon Tetrachloride

Autocatalytic Nature and the Overall Kinetic Order.—The plot of %bromine acted upon at various time intervals for the anisole—bromine reaction in CCl_4 at 30° in the concentration range of 0.1—0.02*M* is shown in Fig. 2. From the shape of the curves the reaction appears to be autocatalytic in nature. The autocatalysis becomes significant after 10, 30 and 60 minutes from the start of the reaction, corresponding to the initial concentrations of 0.10, 0.05 and 0.02*M*, respectively.

The overall order is three for 4—8% reaction, as well as 40—60% reaction, indicating that both the uncatalysed and the autocatalysed bromination of anisole in CCl_4 are kinetically of third order.

FIG. 2



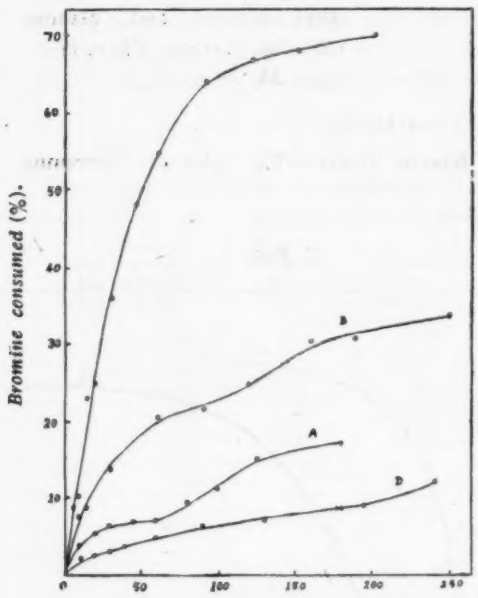
A-0.10*M*. B-0.05*M*. C-0.02*M*.

Effect of Initially-added Hydrogen Bromide.—A saturated solution of HBr in CCl_4 was prepared and its concentration was found to be 0.19*M* by titration with a standard NaOH solution. A 0.02*M* solution of bromine in the above medium was allowed to react with 0.02*M* anisole in CCl_4 at 30°. The rate of bromine consumption was observed to be considerably higher than that of the reaction at the same concentration (0.02*M*) of anisole and bromine, but without the initially-added hydrogen bromide. It may therefore be inferred that hydrogen bromide is a good catalyst for the bromination of anisole in CCl_4 and that the autocatalysis in this reaction is due to the HBr formed in the initial stages.

Activation Energy.—From the kinetic data for the reaction at 0.02*M* in the range of 10°-30°, the time values required for 6% reaction, when autocatalysis would be negligible, were determined, and using them, the activation energy was found to be −8.48 kcal./mole.

Effect of Pyridine.—Pyridine is known to be a good catalyst for the bromination of aromatic compounds. For example, Cohen ("Practical Organic Chemistry", 1946, p. 155) recommends the use of 0.5 g. of pyridine in the preparation of bromobenzene from 50 g. of benzene and 120 g. of bromine.

FIG. 3



A-No pyridine; B-0.02*M*; C- 0.02*M*; D- 0.2*M*.

A quantitative study of the effect of pyridine on the rate of bromination of anisole in CCl_4 has now been made and the kinetic data are shown in Fig. 3, from which the addition of a small quantity of pyridine (0.002 *M*) is seen to increase markedly the rate, but the reaction is still autocatalytic. When the pyridine and bromine concentrations are equal (0.02*M*), the rate is very high and autocatalysis is not observed. A large excess of pyridine (0.2 *M*), however, reduces the reaction rate considerably, and the reaction becomes only slightly autocatalytic.

It was further observed that pyridine (0.2 *M*) and bromine (0.02 *M*) in CCl_4 did not undergo any reaction even after 3 hours, indicating that pyridine could only act as a catalyst, but could not itself undergo bromination.

Spectrophotometric Studies

Absorption Spectra of Bromine in Aqueous Acetic Acid.—For purposes of the reaction mechanism to be suggested later, it seemed necessary to have some idea of the type of interaction between the halogenating reagent and the solvent, for which the

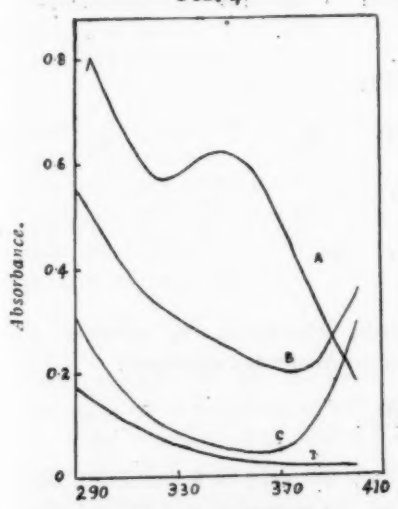
absorption spectra of 0.001*M* bromine in glacial acetic acid and in 75–99% aqueous acetic acid solutions were measured in the region of 2600–8000Å, using a Beckman spectrophotometer, Model DU. In glacial acetic acid, there is an intense absorption at 2600–2800Å and a peak at 4000Å. Buckles and Mills (*J. Amer. Chem. Soc.*, 1953, **75**, 552), who have reported similar results, consider that the UV-absorption is due to bromine-acetic acid charge-transfer complexes, while the absorption maximum at 4000Å is due to uncomplexed bromine molecules.

On increasing the water content of the acetic acid medium from 1 to 25%, it was observed that the intensity of absorption at the peak at 4000Å was almost constant, while that at 2600Å increased two-fold (Table I). This increase in the UV-absorption may be attributed to the greater ease of polarisation of the Br—Br bond in the bromine-acetic acid complexes, caused by an increase of the dielectric constant of the solvent.

The increased polarisation of the Br—Br bond in the presence of water also explains the regular increase in the rate of bromination of anisole with increasing water content of the acetic acid medium, as shown in Table I. Actually the plot of log k_2 against the molecular extinction coefficient at 2600Å for the various aqueous acetic solutions is nearly linear.

The Interaction between Anisole and Iodine.—Keefer and Andrews have established spectrophotometrically the formation of 1 : 1 molecular complexes of chlorine, bromine, iodine and ICl with benzene and its derivatives in CCl_4 medium (*J. Amer. Chem. Soc.*, 1951, **73**, 462 ; 1950, **72**, 4677 ; 1952, **74**, 4500 ; 1955, **77**, 2164, 4202). Recently de Maine has reported the existence of the anisole-iodine complex in the same medium (*J. Chem. Phys.*, 1957, **26**, 1189). But it is doubtful whether such complexes are formed in glacial acetic acid, in which the halogens are polarised into X^+X^- by complexing with the solvent molecules (Fairbrother, *J. Chem. Soc.*, 1948, 1051 ; Mulliken, *J. Amer. Chem. Soc.*, 1950, **72**, 600 ; Buckles and Mills, *loc.cit.*). To verify this the visible and UV-absorption spectra of anisole and benzene in the presence of iodine and bromine in both glacial acetic acid and CCl_4 have been measured.

FIG. 4.



A– 0.1*M* anisole + 0.0037*M* I in CCl_4.
B– ,, ,, + 0 0035*M* I in AcOH.
C– ,, 0 0035*M* I in AcOH.
D–0.0027*M* I in CCl_4.

In Fig. 4 are shown the UV-absorption spectra of mixtures of iodine (0 0037*M*) and anisole (0.1*M*) together with the spectra of iodine alone in the two solvents. In CCl_4 the anisole-iodine mixture shows three absorption peaks, one in the visible region at 5200Å due to molecular iodine, and two in the UV region at 2960Å and 3450Å, due to anisole-iodine molecular complex, in agreement with the results reported by de Maine (*loc.cit.*). But in glacial acetic acid, anisole-iodine mixture has no absorption peak in the UV region ; it has

only a peak at 4800Å corresponding to molecular iodine. This seems to indicate clearly that a molecular complex between anisole and iodine is not likely to be formed in glacial acetic acid.

Interaction of Benzene with Iodine and Bromine.—In CCl_4, a mixture of benzene (0.1*M*) and iodine (0.001*M*) has two absorption maxima, viz., at 2910Å a d 5200Å, due to benzene-iodine complex and iodine molecules, respectively. In glacial acetic acid, on the other hand, a mixture of benzene (0.1*M*) and iodine (0.001*M*) shows only one absorption peak at 4800Å due to molecular iodine, indicating the absence of a benzene-iodine complex in this medium.

Spectrophotometric measurements on the anisole-bromine molecular complex cannot be made because of the fairly fast reaction between anisole and bromine in glacial acetic acid. However, it is possible to secure some information on this point by studying the benzene-bromine molecular complex. A mixture of benzene (0.1*M*) and bromine (0.001*M*) has an absorption peak at 2870Å in CCl_4, but not in glacial acetic acid so that there is little indication of the benzene-bromine complex in the latter solvent, but a definite indication of its formation in CCl_4. From this it can be inferred that the anisole-bromine molecular complex may be formed in CCl_4, but not in glacial acetic acid.

DISCUSSION

Mechanism in Glacial Acetic Acid.—The results, reported earlier regarding the dependence of the kinetic order and the activation energy on the initial concentration of the reactants, temperature and polarity of the medium, are in agreement with Robertson's observations (*loc.cit.*) on the bromination of acetanilide in glacial and aqueous acetic acid. The reaction mechanism postulated by him to interpret the experimental facts, namely,

$$AH + Br_2 \underset{k_2}{\overset{k_1}{\rightleftharpoons}} AH, Br_2$$

$$AH, Br_2 + Br_2 \xrightarrow[k_3]{} AHBr^+ + Br_3^-$$

$$AHBr^+ \xrightarrow[\text{fast}]{} ABr + H^+$$

$$H^+ + Br_3^- \xrightarrow[\text{fast}]{} HBr + Br_2$$

is not satisfactory for two reasons.

Firstly, the occurrence of second and third order kinetics in the reaction is attributed to $k_3 \gg k_2$ and $k_2 \gg k_3$, respectively, in the final rate-expression :

$$\frac{d[AH]}{dt} = \frac{k_1 k_3 [AH][Br_2]^2}{k_2 + k_3[Br_2]}$$

where, the k's are the constants for the reaction steps proposed by Robertson. But how exactly the changes in the initial concentration of the reactants and the polarity of the medium affect the relative values of k_2 and k_3 is not clear.

Secondly, in a polar solvent, like acetic acid, a molecular complex between bromine and the aromatic compound of the type $AHBr_2$, proposed by Robertson,

is not likely to be formed, as pointed out earlier by the present authors (*loc. cit.*) and now confirmed by our study of the absorption spectra of bromine and iodine in the presence of benzene and anisole. Hence, the reaction mechanism in acetic acid can involve only an activated complex of anisole and bromine, whereas in CCl_4, anisole-bromine molecular complex may participate in the reaction. Also, the non-existence of a molecular complex in acetic acid accounts for the absence in this solvent of a negative temperature coefficient, observed in the bromination of mesitylene (Keefer, *et al.*, *loc. cit.*), phenol (Yeddanapalli and Guanapragasam, *loc. cit.*) and anisole in CCl_4, and attributed to the thermal decomposition of the molecular complex.

The observed changes in the order of the reaction under different experimental conditions can satisfactorily be explained by the following mechanism, which is similar to the one proposed by us for the bromination of phenol :

$$C_6H_5.OCH_3 + Br_2 \xrightarrow[\text{slow}]{k} [C_6H_5.OCH_3{}^+Br^-Br] \xrightarrow[\text{(activated complex)}]{Br_2} C_6H_5\,OCH_3{}^+Br + Br_3^-$$

$$C_6H_5.OCH_3{}^+Br \xrightarrow[\text{fast}]{} CH_3O.C_6H_4Br + H^+$$

$$H^+ + Br_3^- \xrightarrow[\text{fast}]{} HBr + Br_2.$$

The function of the second molecule of bromine in the rate-determining step is to facilitate the polarisation of bromine in the activated complex and the subsequent elimination of the Br^- as Br_3^-.

The rate of formation of *p*-bromoanisole, which is the main product, 95%, of the bromination of anisole by bromine in glacial acetic acid (de la Mare and Vernon, *loc. cit.*) is given by

$$d[CH_3O.C_6H_4Br]/dt = k\,[C_6H_5.OCH_3][Br_2]^2$$

which is in agreement with the observed overall third order kinetics at 0.1 *M* and the individual order of 1 for anisole and approximately 2 for bromine.

At lower concentrations of the reactants (0.001 *M*), the bromine in the activated complex will be sufficiently polarised by interaction with the solvent molecules, so that the elimination of the Br^- can take place without further polarisation by a second bromine molecule. The rate-determining step will then be

$$C_6H_5.OCH_3 + Br_2 \xrightarrow[\text{slow}]{k} [C_6H_5.OCH_3{}^+Br^-Br] \xrightarrow[\text{(activated complex)}]{} C_6H_5.OCH_3{}^+Br + Br^-$$

This accounts for the approximately second-order kinetics at 0.001*M*, and the individual order of 1 for both anisole and bromine.

The fractional value of 2.6 for the overall order at an intermediate concentration (0.01 *M*) must be due to the simultaneous occurrence of second and third order reactions, the rate-equation being

$$d[CH_3O.C_6H_4Br]/dt = k_2[C_6H_5.OCH_3][Br_2] + k_3[C_6H_5\,OCH_3][Br_2]^2.$$

Evidence for this composite mechanism is provided by the energetics of the reaction. In glacial acetic acid the activation energy at 0.04 *M*, when the overall order is is 3, is 4 04 kcal./mole and at 0.001 *M*, when the order is 2.3, it is 9.92 kcal./mole.

Increase of temperature will favour therefore the second order reaction, and if the composite mechanism is correct, the order must decrease with rising temperature. Actually the overall order in the concentration range of 0.01-0.005 *M* decreases from 2.66 at 30° to 2.29 at 50°.

Mechanism in Aqueous Acetic Acid.—The mechanism of the bromination of anisole in aqueous acetic acid is essentially similar to the one proposed for the reaction in glacial acetic acid. It has been established by Bradfield *et al.* (*loc. cit.*) and by Berliner and Beckett (*loc. cit.*) that bromination in aqueous acetic acid involves only free molecular bromine, without the participation of such species as HOBr, CH_3COOBr, H_2OBr^+ or $CH_3COOHBr^+$.

Spectrophotometric studies show that the addition of water to the glacial acetic acid medium increases the polarisation of the bromine molecule, thus facilitating the removal of the bromide ion from the activated complex in the rate-determining step of the reaction mechanism. This explains the high rate of bromine consumption in aqueous acetic acid, as well as the predominance of second-order kinetics.

The activation energy of the reaction in 97% aqueous acetic acid increases from 4.4 kcal./mole at 0.04 *M* to 7.7 kcal./mole at 0.001 *M*, and this must be due to the decreasing participation of the third order reaction, as indicated by the fall in the overall order of the reaction from 2.5 to 2.1, when the concentration of the reactants decreases from 0.04 to 0.001 *M*.

Mechanism in Carbon Tetrachloride.—The third-order kinetics, observed in the initial stages of the bromination of anisole in CCl_4, can readily be explained on the basis of the mechanism proposed earlier for the phenol-bromine reaction in the same solvent (*loc. cit.*). In the later stages of the reaction, when autocatalysis is observed, the rate-determining step will involve the elimination of the Br^- from the anisole-bromine molecular complex under the catalytic influence of HBr.

$$C_6H_5.OCH_3,Br_2 + HBr \underset{\text{slow}}{\overset{k'}{\rightarrow}} C_6H_5.OCH_3{}^+Br + HBr_2{}^-.$$

The catalytic effect of pyridine, when its concentration is equal to or less than that of bromine, may be attributed to the participation in the rate-determining step of the polar compound, pyridinium bromide (C_5H_5NHBr), which is formed by the interaction of pyridine and the HBr, produced in the course of the reaction.

$$C_6H_5.OCH_3,Br_2 + C_5H_5NHBr \overset{\text{slow}}{\rightarrow} C_6H_5.OCH_3{}^+Br + C_5H_5NHBr_2{}^-$$

The slow rate of bromination of anisole, when pyridine is present in large excess, is the result of decrease in the concentration of free bromine, and hence, of the anisole-bromine molecular complex, due to the formation of the addition compound C_5H_5N,Br_2.

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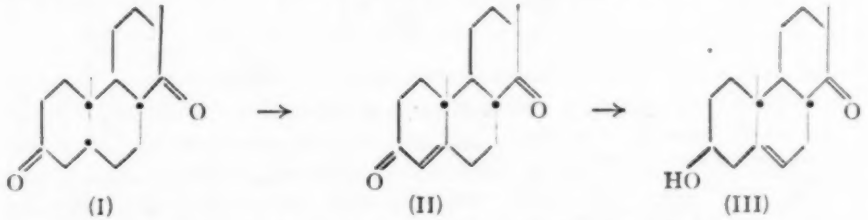
STUDIES IN MICHAEL CONDENSATION. PART V. SYNTHESIS OF 2:4bβ-DIMETHYL-1:7-DIKETO-1:2:3:4:4aα:4b:5:6:7:9:10:10aβ-DODECAHYDROPHENANTHRENE

By Amalendu Banerjee, Barid Baran Mukherjee and Bidyut Kamal Bhattacharyya

2:4b-Dimethyl-1-hydroxy-7-keto-1:2:3:4:4a:4b:5:6:7:9:10:10a-dodecahydrophenanthrene, on oxidation, affords (±) 2:4bβ-dimethyl-1:7-diketo-1:2:3:4:4aα:4b:5:6:7:9:10:10aβ-dodecahydrophenanthrene, stereochemically identical with the diketone (II), obtained by the Oppenauer oxidation of the Köster Logemann ketone. The aforementioned (±) diketone (II) is also obtained by the action of methoiodide of 1-diethylaminobutan-3-one on the methylanilinomethylene derivative of 2:5-dimethyldecalin-1:6-dione.

In their classical synthesis of cholesterol, Robinson and his collaborators (*J. Chem. Soc.*, 1946, 676; 1949, 1855; 1953, 361) have synthesised Reich's diketone (I) (*Helv. Chim. Acta*, 1945, **28**, 892) which has been converted through the unsaturated diketone (II) (Köster Logemann, *Ber.*, 1940, **73**, 299; Billeter and Miescher, *Helv. Chim. Acta*, 1950, **33**, 388) into the Köster Logemann ketone (III). Robinson has described this synthesis of non-aromatic steroid as "formal total synthesis", because products derived from degradation have been utilised as the starting material at the tricyclic stage, for furthering the progress of building up of ring D in steroid.



(I) (II) (III)

In the present paper the synthesis of (±) diketone (II) has been described.

2:4b-Dimethyl-1-hydroxy-7-keto-1:2:3:4:4a:4b:5:6:7:9:10:10a-dodecahydrophenanthrene (IV) (Banerjee and Bhattacharyya, this *Journal*, 1958, **35**, 467) was oxidised with chromium trioxide complex in pyridine according to the method of Sarett *et al.* (*J. Amer. Chem. Soc.*, 1953, **75**, 422) to furnish a viscous oil which, on chromatography, afforded 2:4bβ-dimethyl-1:7-diketo-1:2:3:4:4aα:4b:5:6:7:9:10:10aβ-dodecahydrophenanthrene (II), m.p. 96°, λ_{max} 239 mμ (ε 16,600). With a view to studying the course of the Mannich-Robinson reaction, the methylanilinomethylene derivative of 2:5-dimethyldecalin-1:6-dione was condensed with the methoiodide of 1-diethylaminobutan-3-one, and from the reaction product, the aforementioned unsaturated diketone (II) was isolated in poor yield.

Johnson (*Chem. & Ind.*, 1956, 167) suggested that the incoming alkyl group should take up an axial position in the case of alkylation of unhindered ketone.

On this basis and on the assumption that (V) and (VI) have *trans* ring-fusion (Banerjee and Bhattacharyya, *loc. cit.*), the hydroxyketone (IV) and 2:4b-dimethyl-1:7-diketo-1:2:3:4:4a:4b:5:6:7:9:10:10a-dodecahydrophenanthrene should have a *syn* back-bone. But, as the compounds (V) and (VI) have substituents (cf. Wettstein *et al.*, *Helv. Chim. Acta*, 1957, **40**, 323), it is expected that the aforementioned products of the Mannich-Robinson reaction should be a mixture, which is indeed, the case.

Fortunately, the crystalline ketone (II), isolated from the oxidation of (IV), has been proved by comparison of infra-red spectra to be stereochemically identical with the one obtained by the Oppenauer oxidation of the Köster Logemann ketone (III). Thus, the synthetic unsaturated diketone (II) possesses *anti* back-bone and a *trans* B/C ring-fusion.

FIG. 1

Naturally derived (II) *in chloroform solution.*

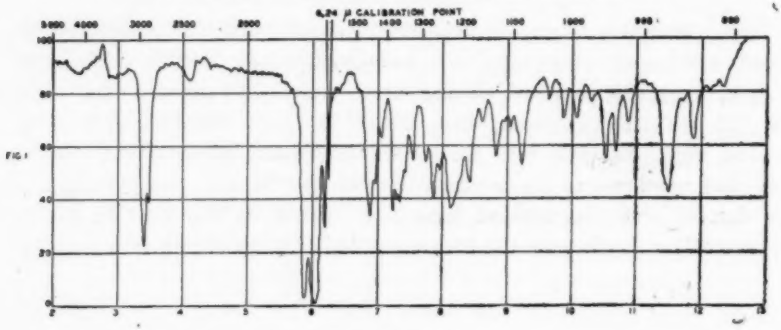
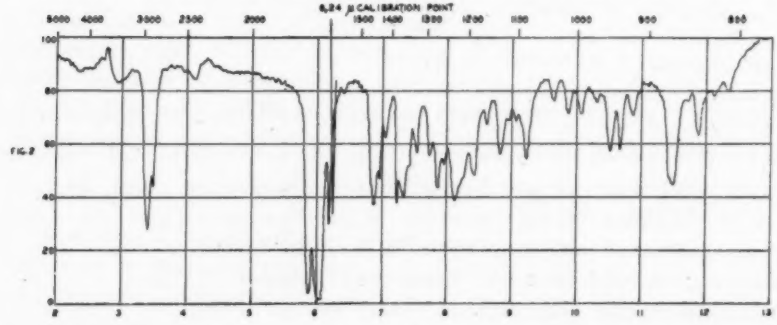


FIG. 2

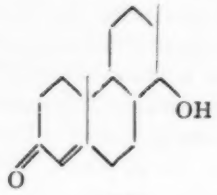
Synthetic (II) *in chloroform solution.*



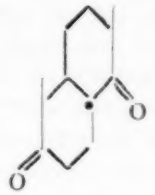
The naturally derived (II) and the hydroxyketone (IV), on treatment with lithium aluminium hydride, followed by heating with 30% Pd on C, afforded 2-methylphenanthrene (VII), identified as its picrate.

It should be mentioned that the comparison of the ultraviolet absorption of the keto-ester (VIII ; R = H), λ_{max} 284 mμ (ϵ 46) and the crystalline bromo compound (VIII : R = Br), λ_{max} 312 mμ (ϵ 92) (Banerjee and Bhattacharyya, *loc. cit.*) clearly

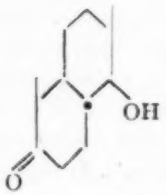
indicates that the bromine atom is axial (Cookson, *J. Chem. Soc.*, 1954, 282; Barton *et al.*, *ibid*, 1957, 2907). It may be mentioned that a higher yield (64%; cf. Banerjee and Bhattcharyya, *loc. cit.*) of the Michael condensation between ethyl cyanoacetate and methyl β-(2-keto-3-methyl*cyclo*hex-$\Delta^{1:6}$-enyl)-propionate could be obtained in a shorter time by carrying out the reaction according to the procedure of Tsuruta *et al.* (*J. Org. Chem.*, 1953, **18**, 1246).



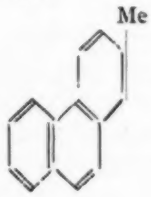
(IV)



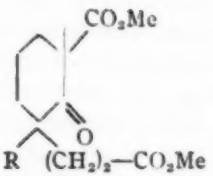
(V)



(VI)



(VII)



(VIII)

EXPERIMENTAL

2 : 4bβ-*Dimethyl* - 1 : 7 - *diketo*-1 : 2 : 3 : 4 : 4aα : 4b : 5 : 6 : 7 : 9 : 10 : 10aβ-*dodecahydrophenanthrene* (II).—(*a*). To a solution of the hydroxyketone (IV, 450 mg.) in dry pyridine (8 c.c.) was added, with shaking, a suspension of chromium trioxide complex, prepared from chromium trioxide (600 mg.) and dry pyridine (6 c.c.). It was shaken well for 30 minutes and then allowed to stand at room temperature for 16 hours. The dark brown reaction mixture was poured into water (150 c.c.) and the precipitated material was extracted thoroughly with ether-benzene. The organic extract was washed successively with HCl (dil.), dilute sodium bicarbonate solution and water, and dried over anhydrous sodium sulphate. After removal of the solvent, the residue (350 mg.) was evaporatively distilled to furnish a viscous colorless oil (300 mg.), b.p. 110-15°/0.2 mm, λ_{max} 239 mμ (ε 9,150), which could not be induced to crystallise. The oil was chromatographed on alumina (9 g.) to afford (*i*) a viscous colorless oil (130 mg.), λ_{max} 240 mμ (ε 12,000), eluted with petroleum ether (40-60°) and (*ii*) pale yellow solid (110 mg.), eluted with 10% benzene in petroleum ether (40-60°).

Fraction (*ii*) was crystallised once from petroleum ether (40-60°) to afford long pale yellow needles (100 mg.), m.p. 95-96°, which was again chromatographed

* The UV spectra have been determined in 95% ethanol by Unicam spectrophotometer, S. P. 500. Analyses of some of the compounds were done by Mrs. C. Datta, University College of Science and Technology, Calcutta.

on alumina (3 g.). The portion eluted with 10% benzene in petroleum ether (40-60°) soon solidified (90 mg.) which, on two crystallisations from the same solvent, furnished colorless needles of the diketone (II), m.p. 96°, λ_{max} 239 mμ (ε 16,600). (Found: C, 77.70; H, 9.28. $C_{16}H_{22}O_2$ requires C, 78.02; H, 9.01%).

A mixture of the crystalline diketone (II, 12 mg.), 2:4-dinitrophenylhydrazine (20 mg.), acetone-free methanol (2 c.c.) and HCl (conc., 1 drop) was heated on the steam-bath for 5 mins. It was cooled and the precipitated red solid was filtered, dried (20 mg., m.p. 230-34°, decomp.) and chromatographed on alumina (600 mg.) using benzene as a solvent. After removal of the solvent, the residue was crystallised four times from ethyl acetate to afford the pure 2:4-dinitrophenylhydrazone as long red needles (12 mg.), m.p. 238-39° (decomp.), λ_{max} 380 mμ (ε 30,200). (Found: N, 13.70. $C_{22}H_{26}O_5N_4$ requires N, 13.12%).

Fraction (*i*), on attempted purification through 2:4-dinitrophenylhydrazone, did not furnish any well-defined crystalline material.

(*b*). The formylation of the bicyclic diketone (V, 1.1 g.) was carried out with sodium dust (250 mg.), absolute methanol (0.4 c.c.), dry thiophene-free benzene (10 c.c.) and ethyl formate (1 c.c.) under nitrogen. The crude formylated product (1.2 g.), developing an intense violet coloration with alcoholic ferric chloride, on treatment with monomethylaniline (0.9 c.c.) and dry thiophene-free benzene (50 c.c.), afforded a yellowish brown methylanilinomethylene derivative (1.7 g.), which was condensed in dry thiophene-free benzene (20 c.c.) with the methoiodide of 1-diethylaminobutan-3-one, prepared from the base (710 mg.) and methyl iodide (0.8 c.c.) in presence of potassium butoxide[t], prepared from potassium (210 mg.) and butanol[t] (5 c.c.). The dark brown reaction product (1.5 g.), on treatment with 10% HCl, followed by 20% aqueous KOH, furnished a black semi-solid residue (800 mg.) which, on evaporative distillation, afforded (*i*) b.p. 90-95°/0.2 mm., 300 mg, identified as the original diketone (V) through its 2:4-dinitrophenylhydrazone, and (*ii*) b.p. 120-25°/0.2 mm, λ_{max} 239 mμ (ε 9,350), a viscous pale yellow oil (150 mg.), a portion (50 mg.) of the which, on treatment with 2:4-dinitrophenylhydrazine, furnished a deep red oil which resisted crystallisation.

Fraction (*ii*) (200 mg.), on chromatography on alumina (6 g.), afforded a viscous colorless oil (100 mg), λ_{max} 239 mμ (ε 9,150), evaporatively distilling at 115-20°/0.2 mm, which was eluted with petroleum ether (40-60°), and a solid material (50 mg.), m.p. 91-92°, eluted with 10% benzene in petroleum ether (40-60°). Two crystallisations of this solid from petroleum ether afforded the pure diketone (II, 35 mg.), m.p. 96°. The m.p. remained undepressed on admixture with the tricyclic diketone, obtained under (*a*). Furthermore, a mixture of the diketone (II, 3 mg. each), obtained under (*a*) and (*b*), was crystallised from the same solvent to afford long colorless needles, m.p. 96°.

(*c*). The hydrolysis of the Köster Logemann ketone acetate (950 mg.), following the procedure of Robinson *et al.* (*loc. cit.*, 1953) afforded the ketone (730 mg.), m.p. 131-32°, the Oppenauer oxidation of which was carried out according to Eastham and Teranishi ("Org. Syn.", Vol. 35, p. 39).

Toluene (30 c.c.) in a three-necked flask was boiled until 2 c.c. of it distilled over. A solution of the ketone (III, 620 mg.) in a mixture of freshly distilled *cyclo*hexanone (4.2 c.c.) and toluene (2 c.c.) was added dropwise to the boiling solution and the distillation was continued to obtain more distillate (5 c.c.). To this boiling solution was added, with stirring, a solution of aluminium propoxide[1] (300 mg.) in toluene (10 c.c.) during 10 mins. The dropping funnel was washed down with toluene (5 c.c.) into the reaction flask. The reaction mixture gradually turned orange-yellow and the boiling was continued for 1½ hours when the distillate (150 c.c.) was collected; the dropwise addition of toluene (150 c.c.) was continued all the while. To the cold reaction mixture was added a saturated solution of sodium potassium tartrate (8 c.c.) and the toluene was completely removed by steam distillation. The residue, cooled in ice, was acidified with H_2SO_4 (very dilute) and the white precipitate was extrated with ether (250 c.c.) which was washed with dilute sodium bicarbonate solution and water and then dried over anhydrous sodium sulphate. The residue, obtained after removal of the solvent, was treated with methanol (10 c.c.), warmed and filtered. The filtrate on concentration (3 c.c.) afforded stout colorless crystals (250 mg.), m.p. 138-39°. Another crop (100 mg.), m.p. 136-38°, was also obtained on further concentration. The residual oily material (225 mg.) was chromatographed on alumina (7.5 g.) and the fraction, eluted with benzene-petroleum ether (40-60°, 1:1), furnished crystals (140 mg.), m.p. 136-38°. The total yield was 79-80%. This material, on further purification through chromatography and crystallisations from methanol, afforded the pure material, m.p. 139-40°, $\lambda_{max.}$ 240 mμ (ε 17,800), $[\alpha]_D^{chf.}$ + 127.1° (lit. records m.p. 140-41°, $[\alpha]_D^{chf.}$ + 128°). (Found: C, 78.57; H, 9.62. Calc. for $C_{16}H_{22}O_2$: C, 78.02; H, 9.01%).

Picrate of 2-Methylphenanthrene.—(*a*). The naturally derived diketone (II, 250 mg.) was reduced with $LiAlH_4$ (300 mg.) in ethereal solution (50 c.c.) by the method described before (Banerjee and Bhattacharyya, *loc. cit.*) and the reaction product was evaporatively distilled to afford a viscous oil (200 mg.), b.p. 130-35°/0.2 mm. A portion of the latter (150 mg.) in a Heymann's apparatus was heated with 30% Pd-C (20 mg.), in an atmosphere of nitrogen, at 310-20° for 1 hour and, then at 325-35° for another hour. The reaction product was extracted with hot benzene. The solution showing a strong green violet fluorescence was evaporated to furnish a tarry residue (125 mg.) which was evaporatively distilled to afford a brownish oil (50 mg.), b.p. 110-15°/0.2 mm. The latter on treatment with saturated ethanolic solution of picric acid (50 mg.) furnished a picrate (60 mg.), m.p. 112-15° which, on two crystallisations from ethanol, afforded the pure material (25 mg.), m.p. 118°. (Found: N, 9.79. Calc. for $C_{21}H_{15}O_7N_3$: N, 9.96%).

The diol (140 mg.), m.p. 175-85° (Robinson *et al.*, *loc. cit.*), obtained by reduction of (III) by $LiAlH_4$, did not furnish 2-methylphenanthrene on dehydrogenation with 10% Pd-C.

(*b*). The hydroxyketone (IV, 150 mg.) was similarly reduced and the oily product (130 mg.), evaporatively distilling at 140-45°/0.3 mm, was dehydrogenated over 30% Pd-C (20 mg.) under identical condition to furnish an oil (50 mg.) which afforded

a picrate (10 mg.), m.p. 110-12°. Two crystallisations from ethanol furnished yellow crystals, m.p. 116-17°, the m.p. of which remained undepressed on admixture with the authentic picrate prepared under (*a*).

Authors' grateful thanks are due to Professor W. S. Johnson of the University of Wisconsin, U.S.A. and Dr. A. Wettstein and Dr. G. Anner of Ciba Limited, Switzerland, for the infra-red spectra and a generous gift of the Köster Logemann ketone acetate, respectively.

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BEHAVIOUR OF ELECTROLYTES IN MIXED SOLVENTS. PART V. CONDUCTANCE OF $MgCl_2$ AND K_2SO_4 IN DIOXANE-WATER MIXTURES AT 35°

By P. B. Das, P. K. Das and D. Patnaik

The conductance of the solutions of magnesium chloride and potassium sulphate in 10, 20 and 30% dioxane-water mixtures by weight has been measured at 35°. Adopting the method of Jenkin and Monk, the dissociation constants and diameters of the ion pairs, $MgCl^+$ and KSO_4^-, have been computed.

Formation of ion association or incomplete dissociation of electrolytes in solutions has been reported from the study of their conductance in various solvents (Harned and Owen "The Physical Chemistry of Electrolytic Solution", 2nd ed., p. 147; James, *J. Chem. Soc.*, 1951, 153; Dunsmore and James, *ibid.*, 1951, 2925; Griffith and Lawrence, *ibid.*, 1955, 1208). The conductance of magnesium chloride, a bimonovalent salt and that of potassium sulphate, a monobivalent electrolyte, in 10, 20 and 30% dioxane-water mixtures has been measured at 35°. This study has been undertaken with a view to ascertaining the effect of the solvent composition on the diameter of the ion pairs, $MgCl^+$ and KSO_4^-. The ionic diameters have been calculated by both the Stokes' and Bjerrum's methods, the latter requiring the dissociation constants of K_{MgCl^+} and $K_{KSO_4^-}$, which have been evaluated.

Experimental

$MgCl_2$ used was of B.D.H.- AnalaR quality. The sample was analysed for Mg^+ and Cl^- content by standard methods (Vogel, "Text Book of Quantitative Inorganic Analysis", 1948, pp. 454, 476). K_2SO_4 of B.D.H.- AnalaR quality was recrystallised from conductivity water, dried at 200° and stored in vacuum.

Preparation of the solvents, solutions and conductance measurements at 35° have been reported earlier (this *Journal*, 1959, **36**, 410).

Discussion

Righellato and Davies (*Trans. Faraday Soc.*, 1930, **26**, 592) have pointed out that in case of monobivalent electrolytes, equilibria of the type,

$$M_2A \rightleftharpoons 2M^+ + A^{2-} \quad \ldots \quad \ldots \quad (1a)$$

$$A^{2-} + M^+ \rightleftharpoons MA^- \quad \ldots \quad \ldots \quad (1b)$$

exist; the dissociation constant K for MA^- is

$$K = \frac{[M^+]\,[A^{2-}]}{[MA^-]} \times \frac{f_{M^+} \times f_{A^{2-}}}{f_{MA^-}} .$$

So for the electrolyte K_2SO_4,

$$K_{KSO_4^-} = \frac{[K^+]\,[SO_4^{2-}]}{[KSO_4^-]} \times \frac{f_{K^+} \times f_{SO_4^{2-}}}{f_{KSO_4^-}} \quad \ldots \quad (2a)$$

Assuming a similar type of behaviour to exist in the case of bimonovalent electrolytes, $MgCl_2$,

$$K_{MgCl^+} = \frac{[Mg^{2+}]\,[Cl^-]}{[MgCl^+]} \times \frac{f_{Mg^{2+}} \times f_{Cl^-}}{f_{MgCl^+}} \quad \ldots \quad (2b)$$

where 'f' represents the activity coefficients of the corresponding ions and the square bracket indicates the molar concentrations.

Following the method of calculation adopted by Jenkin and Monk (*J. Chem. Soc.*, 1951, 68), the first stage of dissociation is assumed to be complete, and we have only to deal with the second equilibrium,

$$MgCl^+ \rightleftharpoons Mg^{2+} + Cl^-.$$

Let m represents the molar concentration of $MgCl_2$ and α be the fraction that does not form ion association, then,

$$[MgCl^+] = (1-\alpha)m\ ;$$
$$[Mg^{2+}] = \alpha m\ ;$$
$$[Cl^-] = m(1+\alpha)\ ;$$

so that,

$$K_{MgCl^+} = \frac{\alpha(1+\alpha)m}{1-\alpha} \times \frac{f_{Mg^{2+}} \times f_{Cl^-}}{f_{MgCl^+}} \quad \ldots \quad (2'b).$$

The solution as a whole can be regarded as a mixture of two types of salts : (*i*) bimonovalent $MgCl_2$ yielding Mg^{2+} and Cl^-, and (*ii*) mono-monovalent $MgCl^+$ Cl^-. For the 2—1 electrolyte, the equivalent conductance

$$\Lambda_{2-1} = \Lambda^0_{2-1} - (A_{2-1} + B_{2-1}\Lambda^0_{2-1})\sqrt{I} \quad \ldots \quad (3a)$$

and for the 1 − 1 electrolyte,

$$\Lambda_{1-1} = \Lambda^0_{1-1} - (A_{1-1} + B_{1-1}\Lambda^0_{1-1})\sqrt{I} \quad \ldots \quad (3b)$$

where A and B are the Onsager constants, Λ^0 is the equivalent conductance at zero concentration and Λ, that at the actual ionic strength, I, where

$$I = \tfrac{1}{2}\{[Cl^-] + [MgCl^+] + 4[Mg^{2+}]\} = m(1+2\alpha) \quad \ldots \quad (4).$$

If k_{2-1} and k_{1-1} are specific conductance of the 2 − 1 and 1 − 1 types of salts respectively, then

$$k_{2-1} = \frac{2\alpha m \Lambda_{2-1}}{10^3} \quad \text{and}$$

$$k_{1-1} = \frac{(1-\alpha)m\ \Lambda_{1-1}}{10^3}.$$

If 'k' is the specific conductance of the electrolyte which now behaves as a mixture of two types, then,

$$k = k_{2-1} + k_{1-1} = \{2\alpha m\ \Lambda_{2-1} + (1-\alpha)m\ \Lambda_{1-1}\}\ 10^{-3}$$

$$\therefore\ \Lambda = \frac{10^3 k}{2m} = \alpha\Lambda_{2-1} + \tfrac{1}{2}(1-\alpha)\Lambda_{1-1} \quad \ldots \quad (5)$$

where Λ is the measured equivalent conductance.

The Onsager constants A and B for 2–1 and 1–1 types are calculated theoretically. Λ°_{2-1} has been determined from the extrapolation of the plot of Λ against $\sqrt{C}$. The value Λ°_{1-1} has been calculated by taking the mobility of $MgCl^{+}$ as two-third of the bivalent Mg^{2+} (Righellato *et al.*, *loc. cit.*) and by making use of the mobility of the Cl^{-}, determined by us (this *Journal*, 1957, **34**, 56). Now the two unknown quantities are α and I. For determination of α, the method of approximation is as follows. Let α be equal to unity, when an approximate value I is calculated according to equation (4). Using this value of I, the value of α can be calculated from equation (5) This value of α is used for calculating a truer value of I, and this process is repeated till a constant value of α is obtained. By using this constant value of α and the activity coefficients calculated from the usual Debye-Hückel expression, the dissociation constants at various concentrations have been determined according to equation (2′b). The same procedure was followed for the ion pair KSO_4^{-}.

TABLE I

Salts :	$MgCl_2$			K_2SO_4		
Solvent comp.:	10% Dioxane	20% Dioxane	30% Dioxane	10% Dioxane	20% Dioxane	30% Dioxane
Conc. (equiv./litre).	Λ ohm^{-1} D=66.33	Λ ohm^{-1} D=57.73	Λ ohm^{-1} D=49.19	Λ ohm^{-1} D=66.33	Λ ohm^{-1} D=57.73	Λ ohm^{-1} D=49.19
0.020	126.28	109.10	86.10	...	111.41	83.03
0.018	127.00	110.26	86.20	...	112.37	83.49
0.016	128.02	111.28	87.10	139.49	113.34	84.81
0.014	129.05	112.60	88.41	140.16	114.43	87.01
0.012	130.10	113.88	89.45	142.69	116.19	88.25
0.010	131.80	115.50	91.03	144.87	117.50	89.16
0.008	132.20	115.85	93.93	147.07	119.17	89.67
0.006	135.20	119.50	95.50	149.08	122.30	90.93
0.004	137.60	122.60	98.50	151.15	124.60	95.60
0.000	146.60	135.80	113.60	163.50	136.00	107.50

TABLE II

Salts :	$MgCl_2$				K_2SO_4					
Solvent comp.:	20% Dioxane		30% Dioxane		10% Dioxane		20% Dioxane		30% Dioxane	
Conc. (equiv./litre)	α.	$K\times10^2$.	α.	$K\times10^2$.	α.	$K\times10^2$.	α.	$K\times10^2$.	α.	$K\times10^2$.
0.020	0.9132	6.02	0.8491	2.28	...	...	0.9400	9.01	0.9259	5.16
0.018	0.9154	5.92	0.8481	2.22	...	...	0.9514	10.77	0.9143	4.01
0.016	0.9146	5.57	0.8463	2.09	0.9400	10.07	0.9462	9.22	0.9199	4.48
0.014	0.9178	5.57	0.8506	2.07	0.9457	10.35	0.9432	8.15	0.9414	5.98
0.012	0.9179	5.06	0.8493	2.16	0.9550	11.52	0.9548	9.65	0.9422	5.76
0.010	0.9224	4.85	0.8552	1.88	0.9681	14.81	0.9534	8.45	0.9458	5.71
0.008	0.9210	4.17	0.8315	2.14	0.9784	14.58	0.9682	11.11	0.9492	5.52
0.006	0.9334	3.35	0.8814	1.82	0.9760	13.92	0.9742	9.75	0.9458	4.38
0.004	0.9485	4.18	0.9003	1.87	0.9750	12.46	0.9750	8.87	0.9548	4.14
Mean :		4.96		2.06		12.53		9.44		5.02

The conductance data for $MgCl_2$ and K_2SO_4 have been recorded in Table I. The calculated values of 'α' and 'K' for the two ion pairs $MgCl^+$ and KSO_4^- have been shown in Table II. In Table III the ionic diameters, calculated by two different methods, that of Stokes and Bjerrum (this *Journal, loc. cit.*), have been tabulated.

TABLE III

Solvent composition.	Ion pair: $MgCl^+$		KSO_4^-	
	a Stokes law.	a Bjerrum equation.	a Strokes law.	a Bjerrum equation.
10	...	...	1.44Å	1.13Å
20	1.60Å	1.13Å	1.59	1.38
30	1.74	1.06	2.00	1.76

For solutions of $MgCl_2$ in 10% dioxane-water mixture, α has been found to be unity, indicating that ion association $MgCl^+$ does not occur to any appreciable degree. The values of the ionic diameters, calculated by the two methods, are in good agreement. So far as these values are concerned, it can be stated that the composition of the solution, which might bring any change in the ion atmosphere, does not affect to any noticeable extent the diameter of the ion pairs, $MgCl^+$ and KSO_4^-.

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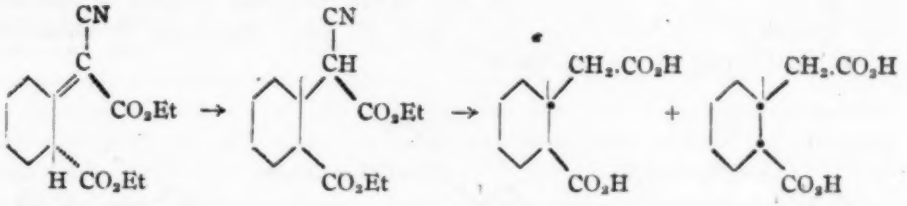
SYNTHESIS OF 1-ACETYL-*cis*-8-METHYLHYDRINDANE

By Shubhabrata Raymahasay, Sisir Kumar Sengupta and Bidyut Kamal Bhattacharyya

Ethyl α-cyano-(2-ethoxycarbonyl-1-methyl*cyclo*hexyl)-acetate, prepared from ethyl α-cyano-(2-ethoxycarbonyl*cyclo*hexylidene)-acetate and MeMgI, has been condensed with ethyl iodoacetate, hydrolysed and decarboxylated and esterified to afford dimethyl 2-methoxycarbonyl-1-methyl*cyclo*hexylsuccinate which, on the Dieckmann cyclisation, followed by hydrolysis and decarboxylation, has furnished an isomeric mixture of 8-methylhydrindan-3-one-1-carboxylic acid which, on the Barbier-Wieland degradation, has afforded *cis*-8-methylhydrindanone-1. The above keto-acid has been converted into 1-acetyl-*cis*-8-methylhydrindane.

The isomerism of substituent at the position-17 in steroid has been studied by various workers (Fieser and Feiser, "Natural Products Related to Phenanthrene", Reinhold Publishing Corporation, 3rd ed., 1949). That similar isomerism is also possible in simpler system is apparent, and one such appropriate system is adequately represented in 1-acetyl-*cis*-8-methylhydrindane, the synthesis of which is described in the present communication.

Ethyl α-cyano-(2-ethoxycarbonyl*cyclo*hexylidene)-acetate (Grewe and Mondon, *Ber.*, 1948, **81**, 279), on treatment with methyl magnesium iodide, afforded ethyl α-cyano-(2-ethoxycarbonyl-1-methyl*cyclo*hexyl)-acetate (Birch and Robinson, *J. Chem. Soc.*, 1943, 501 ; Baltrop and Nicholson, *ibid.*, 1951, 2524), the hydrolysis and decarboxylation of which furnished a mixture of *cis*- and *trans*-2-carboxy-1-methyl*cyclo*hexylacetic acid, m.p. 160° (Clemo and Dieckenson, *ibid.*, 1935, 735 ; Linstead and Millidge, *ibid.*, 1936, 470 ; Johnson *et al.*, *J. Amer. Chem. Soc.*, 1953, **75**, 5963) in 85% yield. This melting point clearly indicates (Linstead and Millidge, *loc.cit.*) the mixture to consist of 60% *cis*-acid (IIIB). Both the acids were isolated in pure state and the *cis*-acid was converted into the *trans*-, following the method of Linstead and Millidge (*loc.cit.*). The preponderance of *cis*-acid over the *trans*- clearly suggests that the addition of methyl has taken place preferentially from the side opposite to the ethoxycarbonyl group attached directly to *cyclo*hexane ring in (I).



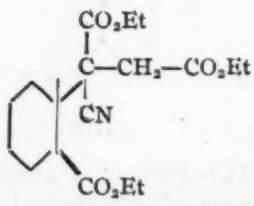
(I) (II) (IIIA) (IIIB)

Ethyl iodoacetate was condensed with the cyano-ester (II), in presence of potassium butoxide[t], to afford ethyl β-cyano-β-ethoxycarbonyl-β-(2-ethoxycarbonyl-1-methyl*cyclo*hexyl)-propionate (IV), which was hydrolysed and decarboxylated with acid, and the

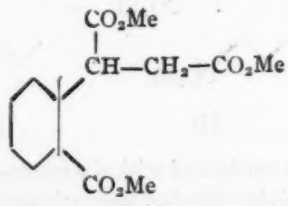
resulting tri-acid was esterified, without purification, to furnish dimethyl 2-methoxycarbonyl-1-methyl*cyclo*hexylsuccinate. The Dieckmann cyclisation of the tri-ester (V) afforded dimethyl 8-methylhydrindan-3-one-1:2-dicarboxylate (VI: R=Me; R_1=CO_2Me) which, on acid treatment, furnished a crystalline keto-acid (VI: R=R_1=H), m.p. 136-37° (A) and a gummy acid (B). The latter, when purified through semicarbazone, afforded a keto-acid, m.p. 74-75°; but this was proved to be a mixture (vide Experimental).

In order to establish the stereochemistry of ring fusion, the keto-acid was reduced according to the procedure of Huang-Minlon (*J. Amer. Chem. Soc.*, 1946, **68**, 2487) to furnish 8-methylhydrindane-1-carboxylic acid (VII: R=H). The methyl ester (VII: R=Me) was converted into (8-methylhydrindan-1-yl)-diphenyl carbinol (VIII). Attempted chromic acid oxidation of the carbinol (VIII) according to the procedure of Zeiss (*ibid.*, 1948, **70**, 868) failed to furnish the expected product. On treatment with potassium hydrogen sulphate, the carbinol was converted into the unsaturated compound (IX), which was ozonised to afford, in 60% yield, 8-methylhydrindanone-1 (Chatterjee and Bhattacharyya, this *Journal*, 1957, **34**, 515 and references cited therein) from which *cis*-8-methylhydrindanone-1 was isolated in 90% yield as semicarbazone, m.p. 225-26° (decomp.).

The acid (VII: R=H), obtained from the aforementioned keto-acid (A), was converted into the acid chloride, which was condensed with sodio enolate of malonic ester according to Wilds and Close (*J. Amer. Chem. Soc.*, 1947, **69**, 3079) and the crude condensation product, on treatment with a mixture of hydrochloric acid and acetic acid, afforded 1-acetyl-*cis*-8-methylhydrindane. The methylketone (XI) furnished a pair of 2:4-dinitrophenylhydrazones, m.p. 169-70° and 105-108°. The acid (VII: R=H), obtained from the aforementioned keto-acid (B), was converted into the methylketone (XI), which also afforded the same pair of 2:4-dinitrophenylhydrazone in the same proportion. It should be pointed out that the lower melting isomer is not a pure compound. This isomerism may be supposed to be due to two epimeric forms of methylketone (XI), epimerism being attributed to the configuration of the acetyl residue about C_1. It has been tacitly assumed that there is no *syn-anti* type of isomerism in the 2:4-dinitrophenylhydrazones (Fehrlin, *Ber.*, 1890, **23**, 1574; Krause, *Ber.*, 1890, **23**, 3617; Overton, *Ber.*, 1893, **26**, 18). In this connection it should be mentioned that Johnson *et al.* (*Proc. Chem. Soc.*, 1957, 58) have synthesised $\alpha\beta$-unsaturated ketone (XII) having a *trans* ring-fusion.



(IV)



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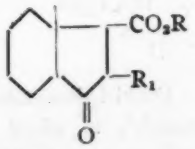
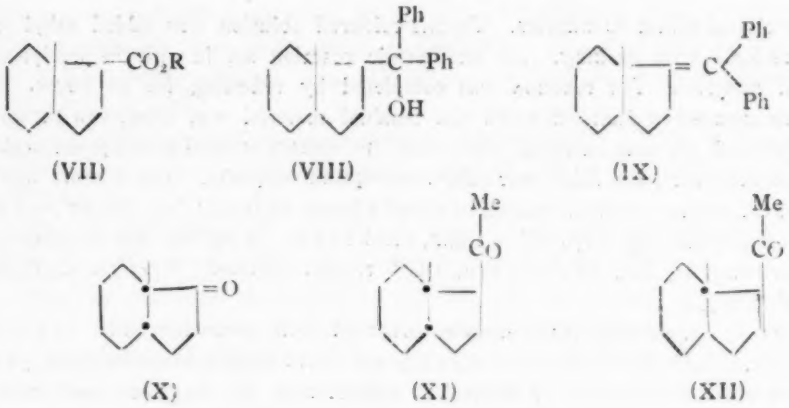


(VI)



(VII) (VIII) (IX)

(X) (XI) (XII)

*EXPERIMENTAL

Ethyl α-Cyano-(2-ethoxycarbonyl-1-methylcyclohexyl)-acetate (1I).—To a stirred solution of the Grignard complex, prepared from MeI (15 c.c.), dry ether (150 c.c.) and magnesium (4.5 g.), was added cuprous chloride (0.3 g.) and stirring was continued for 1 hour. To a stirred solution of the compound (I, 35 g.) in dry ether (200 c.c.), cooled in ice, was added rapidly the above filtered Grignard reagent, when a sticky material separated out. After completion of addition, the reaction was allowed to proceed at room temperature for 1 hour and then refluxed for half-an-hour. After treatment with iced HCl (dil.), the separated oil was extracted with ether, and the extract dried over anhydrous sodium sulphate. The residual yellowish brown oil (35 g.), obtained after evaporation of the ether, was dissolved in 50% ethanol (150 c.c.) and then stirred with sodium cyanide (23 g.) for 1 hour. On dilution of the stirred solution with water (2 litres), the separated oil was extracted with ether and worked up to afford a heavy oil (13 g.), b.p. 128-32°/0.025 mm. (Found: N, 4.96. $C_{15}H_{23}O_4N$ requires N, 4.98%). It was rather convenient to use dry thiophene-free benzene instead of ether to dissolve the compound (I).

Trans & cis-2-Carboxy-1-methylcyclohexylacetic Acids (IIIA & IIIB).—The cyano-ester (II, 2 g.) was refluxed with HCl (conc., 80 c.c.) for 50 hours to furnish a mixture of acids (IIIA and IIIB; 1.2 g., m.p. 160°) which on fractional crystallisation afforded (IIIA, 120 mg.), m.p. 132° (Found: C, 60.02; H, 8.36. Calc. for $C_{10}H_{16}O_4$: C, 59.99; H, 8.06%) and (IIIB, 340 mg.), m.p. 172° (Found: C, 59.70; H, 8.11. Calc for $C_{10}H_{16}O_4$: C, 59.99; H, 8.06%). The pure acid (IIIB, 100 mg.) on being heated with HCl (conc.) for 15 hours at 190-95° in a sealed tube afforded the *trans*-acid (50 mg.), m.p. 132°.

Ethyl β-Cyano-β-ethoxycarbonyl-β-(2-ethoxycarbonyl-1-methylcyclohexyl)-propionate (IV).—(*a*). To potassium butoxide[†], prepared from potassium (2.06 g.) and butanol[†] (41 c.c.) was added dropwise with shaking the cyano-ester (II, 15.2 g.) when a brown

*Ultraviolet spectrum was examined by the Unicam spectrophotometer, S.P. 500, in 95% ethanolic solution.

colour developed within 20 minutes. To this coloured solution was added ethyl iodoacetate (12.6 g.) with shaking. An exothermic reaction set in with the precipitation of a solid material. The reaction was completed by refluxing for 48 hours. The solvent was removed by distillation and the residual material was treated with water. The precipitated oil was extracted with ether, the extract washed with aqueous sodium bicarbonate and water, and dried over anhydrous sodium sulphate. The solvent was removed and the residue was fractionated to afford a heavy oil (12.g.), b.p. 165-82°/0.3 mm, which was redistilled, b.p. 170-80°/0.2 mm, yield 12.2 g. A portion was evaporatively distilled for analysis, b.p. 140°/0.4 mm, n_D^{24} 1.4791. (Found: N, 3.78. $C_{19}H_{29}O_6N$ requires N, 3.81%).

(*b*). To a clear solution of the enolate, prepared from potassium dust (2 g.), dry toluene (37 c.c.) and the cyano-ester (18.53 g.), was added ethyl iodoacetate (12.6 g.) and the reaction was completed first by heating on a water-bath for 10 hours and then by refluxing for 30 hours. On working up and distillation, the condensation product (11.35 g.) was obtained. The use of ethyl bromoacetate lowered the yield to 18.5%.

Dimethyl 2-Methoxycarbonyl-1-methylcyclohexylsuccinate (V).—A mixture of the aforementioned condensation product (IV, 30 g.), glacial acetic acid (150 c.c.) and HCl (conc., 300 c.c.) was refluxed for about 70 hours. The mixture of acids was distilled under reduced pressure and the residue was dissolved in aqueous NaOH and filtered. The alkaline filtrate was acidified with cold HCl and then extracted with ether (six times). On evaporation of the ether and drying, the residue (18 g.) was refluxed with a mixture of methanol (100 c.c.) and H_2SO_4 (*d* 1.84, 18 c.c.) for 50 hours. The ester was worked up with ether and 2*N*-NaOH solution and then distilled to afford a colorless oil (10.7 g.), b.p. 140-45°/0.2 mm. A portion was evaporatively distilled for analysis, b.p. 100°/0.2 mm, n_D^{24} 1.4740. (Found: C, 60.20; H, 8.10. $C_{15}H_{24}O_6$ requires C, 60.02; H, 8.06%).

Dimethyl 8-Methylhydrindan-3-one-1:2-dicarboxylate (VI: R = Me; $R_1 = CO_2Me$).—To sodium methoxide, prepared from sodium dust (1.8 g.), absolute methanol (1.2 c.c.) and dry thiophene-free benzene (15 c.c.), was added, under nitrogen atmosphere, a solution of the trimethyl ester (V, 11.59 g.) in dry thiophene-free benzene (30 c.c.) when an exothermic reaction started. The reaction was allowed to proceed for 1½ hours at the room temperature and then completed by refluxing for further 2 hours. It was cooled, decomposed with iced HCl and extracted with a mixture of ether and benzene. The organic layer was washed with a solution of sodium bicarbonate and water, and dried over anhydrous sodium sulphate. After evaporation of the solvent, the residue was distilled to furnish an oil (7.45 g.), b.p. 138-45°/0.2 mm, which was purified by evaporative distillation, b.p. 100°/0.2 mm, n_D^{33} 1.4820. (Found: C, 62.05; H, 7.84. $C_{14}H_{20}O_5$ requires C, 62.66; H, 7.51%).

8-Methylhydrindan-3-one-1-carboxylic Acid (VI: R = R_1 = H).—The *β*-keto-ester (8.2 g.) was refluxed with HCl (1:1, 150 c.c.) for 16 to 18 hours. The precipitated crystalline material together with adhering oil was extracted thoroughly with ether. After evaporation of the dry solvent, the residual oil was evaporatively distilled to furnish a glassy material (5.91 g.), b.p. 160-70°/0.5 mm, which, on treatment with

ether (20 c.c.) and petroleum ether (60-80° ; 20 c.c.) afforded a solid material which, on crystallisation from either ether or dilute acetic acid, furnished the pure keto-acid (A), m.p. 137-38°, yield 800 mg. (Found : C, 67.13 ; H, 8.37. $C_{11}H_{16}O_3$ requires C, 67.35 ; H, 8.22%).

Its yellow 2 : 4-*dinitrophenylhydrazone* was crystallised from a mixture of ethyl acetate and benzene, m.p. 262° (decomp.). (Found : N, 14.66. $C_{17}H_{20}O_6N_4$ requires N, 14.88%).

The *semicarbazone* was crystallised from a large volume of ethanol, m.p. 264-66° (decomp.) (Found : N, 16.54. $C_{12}H_{19}O_3N_3$ requires N, 16,59%).

The mother-liquors furnished an oil (B, 5 g.) a portion (1.2 g.) of which was converted into the semicarbazone, m.p. 248° (decomp.) (1.1 g.). This was refluxed with a solution of oxalic acid (6 g.) in water (30 c.c.) for 4 hours. The oily reaction product was taken up in ether. The ethereal layer was washed with a solution of calcium chloride and water, dried and evaporated. The residue, on treatment with a mixture of ether and petroleum ether (60-80°), furnished a crystalline acid which was filtered. The filtrate was evaporated and then evaporatively distilled to afford a glassy acid, b.p. 120°/0.2 mm, λ_{max} 286-88 mμ (ε 26). (Found : C, 67.13 ; H, 8.37. $C_{11}H_{16}O_3$ requires C, 67.35 ; H, 8.22%). This solidified on long standing (about a month), m.p. 74-75°.

The above glassy acid furnished a *semicarbazone* which, on repeated crystallisations, afforded the pure material, m.p. 269-72° (decomp.) and did not depress the m.p. of the semicarbazone prepared from the crystalline acid. The 2 : 4-*dinitrophenylhydrazone* of the glassy acid, m.p. 216-20°, could not be made homogeneous by repeated crystallisations.

Nitric acid oxidation of the keto-acid failed to furnish any useful product.

8-*Methylhydrindane*-1-*carboxylic Acid* (VII : R = H).—A mixture of the keto-acid (B, 3.3 g.), 85% hydrazine hydrate (5.4 g.) and diethyleneglycol (16 c.c.) was warmed for 15 mins. and then an aqueous solution of NaOH (3 g. in 6 c.c.) was added. The mixture was heated under mild reflux at 120° for ½ hour. The reflux condenser was taken out and the content was slowly heated to 190° in about 3 hours' time after which the reflux condenser was replaced and the heating continued for further 2 hours at 190-200°. It was cooled, diluted with water (50 c.c.) and acidified with HCl (cold). The precipitated oil was extracted thoroughly with ether. On evaporation of the solvent, the residue was evaporatively distilled to afford an oil (2.5 g.), b.p. 115-20°/0.4 mm. (Found : C, 72.28 ; H, 9.98. $C_{11}H_{18}O_2$ requires C, 72.46 ; H, 9.95%).

A similar reduction of the crystalline keto-acid (A) afforded the expected product in 97% yield.

Methyl 8-*Methylhydrindane*-1-*carboxylate* (VII : R = Me).—The acid (VII : R = H) was esterified with diazomethane in ethereal solution and worked up with NaOH solution ; b.p. 100-02°/0.3 mm, $n_D^{24.5}$ 1.4767. (Found : C, 73.77 ; H, 10.29. $C_{12}H_{20}O_2$ requires C, 73.47 ; H, 10.27%).

(8-*Methylhydrindan*-1-*yl*)-*diphenyl Carbinol* (VIII).—To a solution of the Grignard reagent, prepared from bromobenzene (6.28 g.), magnesium (1 g.), dry ether (30 c.c.)

and methyl iodide (0.5 c.c.), was added a solution of the ester (VII : R = Me ; 2 g.) in benzene (10 c.c.). After allowing it to stand at room temperature for several hours, it was refluxed for one hour and decomposed with an iced solution of ammonium chloride. It was worked up and the material, thus obtained, was refluxed with a solution of NaOH (2 g.) in a mixture of water (5 c.c.) and 95% ethanol (10 c.c.) for 2 hours. The alcohol-water was removed by distillation and the precipitated oil was extracted with ether which was washed with water, and dried. On evaporation of the solvent, the residue was evaporatively distilled : (*i*) 80-110°/0.4 mm, yield 100 mg. (biphenyl) ; (*ii*) 160-70°/0.4 mm, yield 3 g. The viscous material (*ii*) was evaporatively redistilled twice, b.p. 140°/0.3 mm. (Found : C, 86.10 ; H, 9.06. $C_{23}H_{28}O$ requires C, 86.18 ; H, 8.80%).

1-*Diphenylmethylene*-8-*methylhydrindane* (IX).—An intimate mixture of the carbinol (VIII, 1.4 g.) and fused $KHSO_4$ (4 g.), taken in a sublimation tube, was introduced into a preheated chamber at 180° and kept at that temperature for 20 mins. after which it was worked up to afford an oil, which was evaporatively distilled at 115-20°/0.3 mm, yield 1 g., n_D^{25} 1.5550, λ_{max} 249 mμ (ε 12, 590). (Found : C, 91.03 ; H, 8.65. $C_{23}H_{26}$ requires C, 91.33 ; H, 8.67%).

cis-8-*Methylhydrindanone*-1 (X).—Through a solution of the unsaturated compound (IX, 750 mg.) in dry chloroform was passed ozone for 1 hour. The ozonised solution was treated with zinc dust (200 mg.) and acetic acid (0.5 c.c.). After 14 hours at room temperature, it was warmed on the steam-bath for 5 mins. The chloroform solution was washed with water and after evaporation of the solvent, the residue was evaporatively distilled : (*i*) b.p. 120-125°/40 mm, yield 200 mg., m.p. 46°, λ_{max} 255 mμ (ε 15,140), identified as benzophenone through its semicarbazone, m.p. 164-65° ; (*ii*) b.p. 140-50°/40 mm, yield 220 mg., λ_{max} 252 mμ (ε 1,585), showing that the material contained approximately 10% of benzophenone.

The semicarbazone (200 mg.), prepared from fraction (*ii*) (150 mg.), was crystallised from methanol to afford pure crystals, m.p. 225-26° (decomp.), yield 125 mg., identified as the semicarbazone of *cis*-8-methylhydrindanone-1 by mixed m.p., and another crop (25 mg.), m.p. 224-25° (decomp.). (Found : C, 63.03 ; H, 8.93. Calc. for $C_{11}H_{19}ON_3$: C, 63.13 ; H, 9.95%). The residual semicarbazone (30 mg.) was decomposed with oxalic acid to afford the ketone (20 mg.) which was mixed with the ketone (60 mg.) of the aforementioned fraction (*ii*) and chromatographed on alumina (6 g.), when an oil (50 mg.) was obtained which did not show any absorption maxima at 252 mμ. This ketone (40 mg.) afforded the semicarbazone (*i*), m.p. 224-25° (decomp.), yield 30 mg. ; (*ii*), m.p. 208-12° (decomp.), yield 10 mg.

1-*Acetyl*-cis-8-*methylhydrindane* (XI).—To the stirred sodio enolate, prepared from diethyl malonate (18 c.c.), sodium dust (2.9 g.) and dry ether (160 c.c.), was added slowly a solution of the crude acid chloride, prepared from acid (VII : R = H, 4.58 g.), [obtained from the keto-acid B], dry ether (20 c.c.), thionyl chloride (6 c.c.) and pyridine (3 drops), in benzene (17 c.c.) during 80 mins. The stirring was continued for further 2 hours when the content of the flask became a slurry. After allowing it to stand at room temperature for 14 hours, it was refluxed for 1½ hours. It was cooled

in an ice-bath and decomposed with cold dilute acetic acid. The upper organic layer was separated and the aqueous layer extracted with a mixture of ether and benzene. The combined organic extract was washed successively with 2*N*-HCl, sodium bicarbonate and water. On evaporation of the dry solvent, the residue was distilled to remove unchanged malonic ester (14.28 g.), b.p. 80°/3 mm. The residue was refluxed with a mixture of glacial acetic acid (25 c.c.), HCl (conc., 25 c.c.) and water (10 c.c.) for 4 hours. It was worked up with ether, sodium bicarbonate solution and water. After evaporation of the dry solvent, the residue was distilled to afford a colorless volatile liquid (3.51 g.), b.p. 158 62°/40 mm, $n_D^{26.3}$ 1.4852. (Found : C, 79.74 ; H, 10.99. $C_{12}H_{20}O$ requires C, 79.93 ; H, 11.18%).

The *semicarbazone*, m.p. 178-80°, was crystallised twice from 95% ethanol, m.p. 185° (softening at 177°) ; after drying in vacuum, m.p. 188-91° (softening at 186°). (Found : N, 17.70. $C_{13}H_{23}ON_3$ requires N, 17.74%).

The 2 : 4-*dinitrophenylhydrazone* (350 mg.), obtained from the ketone (200 mg.), was purified through chromatography over alumina (10 g.) and treated with hot absolute ethanol, cooled and filtered. The crystalline residue, m.p. 146-60°, on fractional crystallisation from a mixture of ethanol and ethyl acetate, afforded : (*i*) orange needles, m.p. 169-70°, yield 90 mg. [Found (*i*) : N, 15.40. $C_{18}H_{24}O_4N_4$ requires N, 15.52%] ; (*ii*) m.p. 164-70° (100 mg.). The alcoholic filtrate, on concentration, furnished a yellow solid, m.p. 94-100° (70 mg.) which, on fractional crystallisation from methanol, afforded yellow feathers, m.p. 104-109°, in extremely poor yield. [Found (*ii*) : N, 16.20. $C_{18}H_{24}O_4N_4$ requires N, 15.52%). The methylketone (XI), prepared from the keto-acid A, also afforded the same pair of isomeric 2 : 4-dinitrophenylhydrazone in the same proportion. Perbenzoic acid oxidation of the ketone did not furnish any useful product.

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FORMATION OF COMPOUNDS OF ANHYDROUS ALUMINIUM CHLORIDE WITH PHENOLS

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Two series of complex compounds have been prepared from anhydrous aluminium chloride and various phenols in benzene—one having excess of $AlCl_3$ and the other, excess of phenol. The properties of the compounds and thier structures have been studied and discussed.

Menzel and Frohilich (*Ber.*, 1942, **75**, 1055) studied the formation of complex compounds of anhydrous aluminium chloride with ether, and Gmelin (Aluminium B: $AlCl_3$, pp. 213-16) with methyl and ethyl alcohols. Ulich and Heyne (*Z. Elektrochem.*, 1935, **41**, 509) prepared the complex compounds of $AlCl_3$ with aldehydes and ketones, Platnikov and Gorenbein (*Mem. Inorg. Chem. Ukrain Acad. Sci.*, 1936, **3**, 471) and Platnikov and Jankolevitsch (*J. Gen. Chem., USSR.*, 1933, **3**, 802) with esters, acid chlorides, nitro compounds and sulphones, and Asoaka (*J. Chem. Soc., Japan*, 1943, **64**, 541) with olefines. Meisner and French (*J. Amer. Chem. Soc.*, 1952, **74**, 1000) have described the isomerisation of cresols by $AlCl_3$. Dilbe *et al.* (*Research*, London, 1949, **2**, 538) found that $AlCl_3$ with *o*-, *m*- and *p*-xylenes formed the compound $Me_2C_6H_4.AlCl_3$ in each case.

Though a large number of compounds of aluminium chloride with amines, hydrocarbons and various organic compounds are reported in the literature, very little quantitative work has been done on the formation of compounds of aluminium chloride with phenols, substituted or otherwise. The present investigation was therefore undertaken with a view to studying the formation of complex compounds of aluminium chloride with phenols in benzene.

Experimental

Pure anhydrous aluminium chloride and the organic compounds were dissolved in benzene separately and filtered.

Two series of experiments were carried out. In one case, an excess of $AlCl_3$ and in the other, an excess of the organic compound was added till the precipitation was complete. It was left for a few hours, filtered and the precipitate washed with benzene, dried in a steam-oven and analysed.

Aluminium was estimated as Al_2O_3 and chlorine as AgCl. Carbon and nitrogen were estimated in a few cases; the percentage of organic matter was calculated and for the rest, it was found by difference.

All the chemicals used were of B.D.H. or E. Merck's E.P. quality.

TABLE I

Formation of compounds of anhydrous aluminium chloride with phenols in benzene ($AlCl_3$ *in excess*).

No.	Phenols.	Colour.	% Al.		% Cl.		% Org. matter.		% C or N.		Probable formulae.
			Found.	Calc.	Found.	Calc.	Found.	Calc.	Found.	Calc.	
1.	α-Naphthol	Rosy white	9.65	9.75	39.58	38.35	51.69	51.90	C: 43.08	43.27	$AlCl_3.C_{10}H_7OH$
2.	β-Naphthol	Pinkish white	9.70	9.75	39.52	38.35	50.68	51.90	...	...	$AlCl_3.C_{10}H_7OH$
3.	*o*-Cresol	White	11.23	11.18	43.79	44.08	44.56	44.74	C: 34.66	34.81	$AlCl_3.C_6H_4(CH_3)OH$
4.	*m*-Cresol	White	11.20	11.18	43.80	44.08	45.00	44.74	...	...	$AlCl_3.C_6H_4(CH_3)OH$
5.	*p*-Cresol	White (milky)	11.24	11.18	43.78	44.08	44.98	44.74	...	...	$AlCl_3.C_6H_4(CH_3)OH$
6.	Xylenol (1:2:4)	Brown	10.45	10.57	41.80	41.67	47.27	47.76	C: 37.20	37.60	$AlCl_3.C_6H_3(CH_3)_2OH$
7.	Xylenol (1:3:4)	Brown	10.50	10.57	41.78	41.67	47.72	47.76	...	...	$AlCl_3.C_6H_3(CH_3)_2OH$
8.	Benzonaphthol	Milky white	7.04	7.04	28.02	27.92	65.27	65.04	C: 53.69	53.40	$AlCl_3.C_6H_5CO.C_{10}H_7OH$
9.	*o*-Aminophenol	Light grey	14.36	14.37	56.82	56.66	28.82	28.98	...	...	$2AlCl_3.C_6H_4(NH_2)OH$
10.	*m*-Aminophenol	Grey	14.26	14.37	56.90	56.66	28.84	28.98	...	...	$2AlCl_3.C_6H_4(NH_2)OH$
11.	*p*-Aminophenol	Grey	14.40	14.36	56.92	56.66	29.97	28.98	N: 3.85	3.73	$2AlCl_3.C_6H_4(NH_2)OH$
12.	*o*-Nitrophenol	Light blue	13.12	13.30	51.90	52.48	33.26	34.22	N: 3.35	3.45	$2AlCl_3.C_6H_4(NO_2)OH$
13.	*m*-Nitrophenol	Bluish white	13.20	13.30	52.42	52.48	34.38	34.22	...	...	$2AlCl_3.C_6H_4(NO_2)OH$
14.	*p*-Nitrophenol	White	13.28	13.30	52.20	52.48	34.60	34.22	...	...	$2AlCl_3.C_6H_4(NO_2)OH$
15.	Catechol	White	14.20	14.40	56.58	56.80	29.22	28.80	...	...	$2AlCl_3.C_6H_4(OH)_2$
16.	Resorcinol	Light brown	14.26	14.40	56.60	56.80	29.14	28.80	...	...	$2AlCl_3.C_6H_4(OH)_2$
17.	Pyrogallol	Greyish white	13.86	13.74	53.44	54.20	32.37	32.06	C: 18.50	18.33	$2AlCl_3.C_6H_3(OH)_3$

TABLE II

Formation of compounds of anhydrous aluminium chloride with phenols in benzene (phenols in excess).

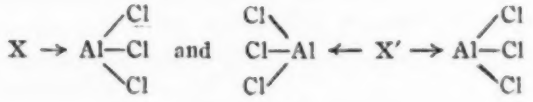
No.	Phenols.	Colour.	% Al.		% Cl.		% Org. matter.		%C or N.		Probable formulae.
			Found.	Calc.	Found.	Calc.	Found.	Calc.	Found.	Calc.	
1.	α-Naphthol	White	6.25	6.41	26.50	25 29	68 16	68.30	C: 56.79	56 97	$AlCl_3.2C_{10}H_7OH$
2.	β-Napthol	Dull white	6.33	6.41	26.61	25.29	67 06	68.30	...	...	$AlCl_3.2C_{10}H_7OH$
3.	*o*-Cresol	Earthy white	7.78	7.73	31.26	30.50	62.04	61.77	C: 48.27	48.09	$AlCl_3.2C_6H_4(CH_3)OH$
4.	*m*-Cresol	Earthy white	7.84	7.73	31.30	30.50	61.16	61.78	...	...	$AlCl_3.2C_6H_4(CH_3)OH$
5.	*p*-Cresol	White	7.82	7.73	31.08	30 50	61.10	61.78	...	...	$AlCl_3.2C_6H_4(CH_3)OH$
6.	Xylenol (1:2:4)	Light brown	7.05	7.16	28.21	28.24	64.85	64.60	C: 51.02	50 84	$AlCl_3.2C_6H_3(CH_3)_2OH$
7.	Xylenol (1:3:4)	Light brown	7.09	7.16	28.09	28 24	64.82	64.60	...	...	$AlCl_3.2C_6H_3(CH_3)_2OH$
8.	Benzonaphthol	White	4.22	4 29	16.78	16 92	78 89	78.79	C: 64.90	64.82	$AlCl_3.2C_{10}H_7(OH)COC_6H_5$
9.	*o*-Aminophenol	Greyish white	11.26	11.14	43.92	43.89	44 82	44.97	...	...	$AlCl_3.C_6H_4(NH_2)OH$
10.	*m*-Aminophenol	Dark grey	11.23	11.14	43.72	43.89	44 62	44.97	N: 5.73	5 76	$AlCl_3.C_6H_4(NH_2)OH$
11.	*p*-Aminophenol	Grey	11.20	11.14	44.02	43 89	44.79	44 97	...	...	$AlCl_3.C_6H_4(NH_2)OH$
12.	*o*-Nitrophenol	Dull white	9 95	9 91	39.54	39.08	50 51	51.01	...	...	$AlCl_3.C_6H_4(NO_2)OH$
13.	*m*-Nitrophenol	White	9.98	9.91	39.34	39.08	50 64	51.01	N: 5.10	5.14	$AlCl_3.C_6H_4(NO_2)OH$
14.	*p*-Nitrophenol	White	10.00	9 91	39.42	39 08	50.58	51.01	...	...	$AlCl_3.C_6H_4(NO_2)OH$
15.	Catechol	White	10 98	11.09	43.89	43.73	44.87	45.18	...	...	$AlCl_3.C_6H_4(OH)_2$
16.	Resorcinol	Light red	11 05	11.09	44.08	43.73	45 63	45.18	C: 29.86	29.58	$AlCl_3.C_6H_4(OH)_2$
17.	Pyrogallol	Grey	10.28	10.53	40.66	41.51	49.06	47.96			$AlCl_3.C_6H_3(OH)_3$

General Properties.—In all the cases, slightly coloured, amorphous, hygroscopic but fairly stable compounds were obtained. Those obtained with phenols having more than one co-ordinating group are more stable than those obtained with phenols having only one such group. In each case, two types of compounds, one with an excess of $AlCl_3$ and the other with an excess of the phenol, were formed, the former being more stable than the latter. The compounds obtained with an excess of $AlCl_3$, when heated, decompose above 200°, but those obtained with an excess of phenol decompose below 200°.

The compounds are not acted upon by cold water, dllute HCl or HNO_3, but are fairly soluble in concentrated HNO_3,HCl and moderately strong NaOH solution. These are soluble in alcohol or acetone and insoluble in benzene, toluene or xylene.

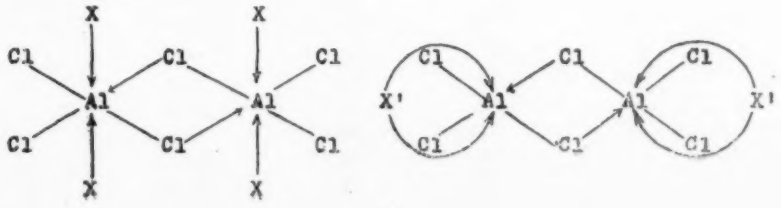
Discussion

An examination of the results show that two series of compounds are formed, one, when an excess of $AlCl_3$, and the other, when an excess of the phenol, is used. Also in each of the above cases, the compounds obtained with phenols having one co-ordinating group and with those having more than one co-ordinating groups are different. In non-co-ordinating medium, like benzene, an equilibrium exists between monomeric and dimeric forms of $AlCl_3$, which is probably responsible for the formation of these two series of compounds. With an excess of $AlCl_3$, two types of compounds, $AlCl_3.X$ and $2AlCl_3.X'$ (where X is a phenol having one co-ordinating group and X′ having two co-ordinating groups), are formed and can be represented respectively as:



In each case the co-ordination number of Al is four and it assumes the inert gas (Argon) configuration. The compounds obtained are fairly stable.

With an excess of phenol, similar results are obtained. Two types of compounds, $AlCl_3.2X$ and $AlCl_3.X'$, are formed, which can be represented as:



The formation of these compounds is probably due to the dimeric form of $AlCl_3$, in which the co-ordination number becomes six, which is the maximum for aluminium. Though the inert gas configuration is not attained in these compounds, but they are fairly stable, which is probably due to the symmetrical structure.

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KINETICS AND MECHANISM OF AROMATIC HALOGENATION: BROMINATION OF ANISOLE WITH IODINE BROMIDE IN GLACIAL ACETIC ACID AND CARBON TETRACHLORIDE

By N. S. Gnanapragasam, N. Venkateswara Rao and Lourdu M. Yeddanapalli

The anisole-iodine bromide reaction shows marked differences in kinetics, energetics and catalytic nature in the two solvents: (*i*) glacial acetic acid and (*ii*) CCl_4. The overall kinetic order is 3 in (*i*), but increases to 4 in (*ii*). The apparent energy of activation is 11.5 kcal./mole between 20° and 40° in (*i*), but has a value of -3.1 kcal./mole in the range of -15.5° to 40° in (*ii*). In (*i*) the catalytic maximum occurs at 0.35 for the ratio of total iodine to total bromine, whereas in (*ii*) it occurs at 0.49 These results are satisfactorily explained by the proposed reaction mechanisms. An equation has also been derived to account for the catalytic maximum observed in IBr-catalysed bromination of aromatic compounds.

In a previous publication (Yeddanapalli and Gnanapragasam, *J. Chem. Soc.*, 1956, 4934) mention was made from some preliminary experiments that the anisole—IBr reaction in CCl_4 was kinetically of third order at 0.02-0.01*M*, with a negative temperature coefficient between 30° and 40°. The present paper deals with the results of a detailed study of the kinetics, energetics and the nature of the IBr-catalysis of anisole—IBr reaction in CCl_4 as well as in glacial acetic acid. The modification of Tsuruta's equation (*J. Amer. Chem. Soc.*, 1952, **74**, 5995) for explaining the catalytic maximum observed in aromatic brominations has also been discussed in the light of fresh experimental data on the bromination of anisole.

Experimental

Anisole, bromine, iodine, glacial acetic acid and CCl_4 were purified according to the procedures described earlier (this *issue*, p. 745). The rate-measurements were made as in the case of the bromination of phenol (Yeddanapalli and Gnanapragasam, *loc. cit.*). Preliminary experiments showed the reaction to be not light-sensitive and quite reproducible.

Results in Carbon Tetrachloride

Overall Kinetic Order.—From the measurements of the rate of halogen consumption in the concentration range of 0.04-0.01*M* at 30°, the overall kinetic order is 4, as seen from the last column of Table I.

Table I

Solvent: CCl_4. Temp. = 30°.

% Halogen consumed.	C_1 (mole/lit.).	C_2 (mole/lit.).	t_1 (sec.).	t_2 (sec.).	n (overall order).
4	0.040	0.020	89	800	4.17
10	0.040	0.020	440	3540	4.01
3	0.020	0.013	540	1920	3.94
5	0.020	0.013	1140	4200	4.03
2	0.020	0.010	330	2460	3.96
4	0.020	0.010	810	7140	4.13

Individual Orders.—The order with respect to IBr was evaluated by the isolation method, using an excess of anisole (0.2*M*) and varying the concentration of IBr from 0.02 to 0.01*M*. From the time values required for 4-10% reaction, the order for IBr is found to be 3. For determining the order with respect to anisole, its concentration was reduced from 0.2 to 0.1*M*, keeping IBr at 0.01*M*. From the kinetic data obtained, the order for anisole is unity.

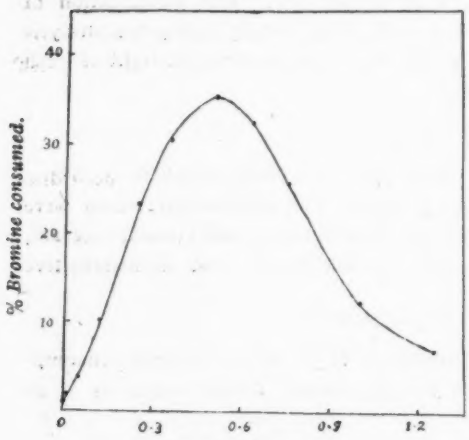
Activation Energy.—The reaction between anisole (0.02*M*) and iodine bromide (0.02*M*) in CCl_4 has a negative temperature coefficient throughout the range of -15.5° to 40°, unlike the phenol—IBr reaction, which in the same solvent has a positive temperature coefficient at 0°-10° and a negative value at 30°-40°, the inversion occurring at 19°. The activation energies, calculated from the slopes of the plots of log $1/t$ against $1/T$ (°K), as described earlier (this *issue*, p. 745), are -3.20 and -3.04 kcal./mole for 8% and 10% reaction respectively, the average being -3.12 ± 0.1 kcal./mole.

Iodine Bromide Catalysis.—In order to examine the effect of iodine on the rate of bromination of anisole in CCl_4, a series of experiments was performed in which the concentration of iodine was progressively increased from 0 to 0.08*M*, the concentration of anisole and total bromine being kept constant at 0.04*M* and 0.02*M*, respectively. The rate of bromination was found to increase in the beginning and then to fall off after reaching a maximum at 0.01*M* of iodine. From Fig. 1, which represents the plot of the percentage of total bromine consumed in the first 3 minutes against the ratio of total iodine to total bromine, it is seen that the rate of bromination is a maximum when this ratio is 0.49. Utilising the value of 331.6 for the equilibrium constant of the reaction:

$$I_2 + Br_2 \rightleftharpoons 2\ IBr$$

at 30° (Yeddanapalli *et al.*, *loc. cit.*), the concentration of IBr and that of free bromine at the catalytic maximum are, respectively, 0.0193*M* and 0.01035*M*, from which the ratio of IBr to free bromine is 1.9, or approximately 2. This seems to suggest that the rate-determining step must include two molecules of IBr as catalyst for each molecule of free bromine, so that the rate-expression may be written as

FIG. 1



$$dx/dt = k\,[C_6H_5.OCH_3]\,[Br_2]\,[IBr]^m \qquad \ldots \quad (1)$$

where $m = 2$.

For confirming the value of '*m*' in the above equation, a further series of experiments were carried out keeping the concentration of anisole and *free* bromine constant at 0.02*M* each, and increasing the IBr concentration from zero to 0.06*M*. The

percentage of free bromine acted upon in the first minute increased steadily with increasing IBr concentration, as can be seen from column 4 of Table II.

TABLE II

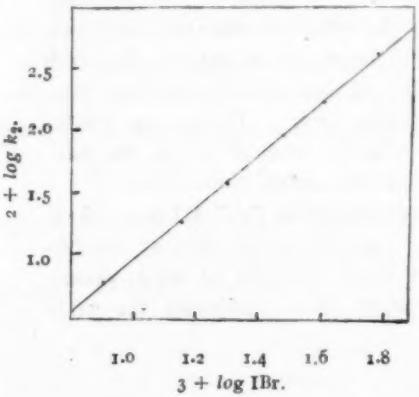
Solvent: CCl_4. Temp. = 30°. Anisole = 0.02*M*. Free bromine = 0.02*M*.

Conc. of total Br.	Conc. of total I.	Conc. of IBr.	% Free bromine consumed in 1 min.	k_2.
0.024*M*	0.004*M*	0.008*M*	3.6	0.0622
0.027	0.007	0.014	10.2	0.1884
0.030	0.010	0.020	18.7	0.3832
0.035	0.015	0.030	35.6	0.9210
0.040	0.020	0.040	51.6	1.7760
0.050	0.030	0.060	72.2	4.3280

The value of '*m*' was calculated by the following procedure. The rate-equation (1) may be written as

$$\frac{dx/dt}{[C_6H_5{\cdot}OCH_3][Br_2]} = k\,[IBr]^m = k_2 \quad \ldots \qquad \ldots \quad (2)$$

FIG. 2



where k_2, for a given constant amount of IBr, can be regarded as a second-order constant dependent only on anisole and bromine concentrations. On taking logarithms, one gets

$$\log k_2 = \log k + m \log [IBr] \quad \ldots \quad (3)$$

so that the plot of log k_2 against log[IBr] must be linear, the slope of the line giving the value of '*m*'. Actually, the plot of log k_2 against log[IBr] (Fig. 2) is a straight line with a slope of 2.09, or nearly 2, thus confirming the rate-equation (1).

Results in Glacial Acetic Acid

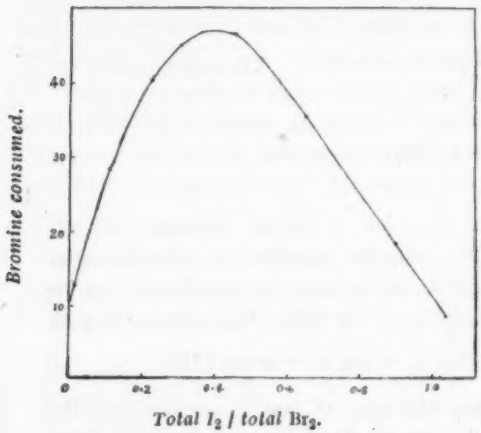
Overall and Individual Kinetic Orders.—The anisole—IBr reaction in glacial acetic acid has an overall kinetic order of 3 in the range of 0.16-0.01*M*. The individual orders calculated from the results of three experiments with anisole and IBr, being respectively 0.2, 0.02 ; 0.2, 0.01 ; 0.1, 0.01*M*, are 2 for IBr and 1 for anisole.

Activation Energy.—Rate-measurements were made at 20-40° using 0.04*M* anisole and IBr solutions and from the results obtained, the time values required for 6, 8 and 10% halogen consumption were calculated. Then, log $1/t$ was plotted against $1/T$ (°K), and from the slopes of the linear plots, the activation energies are found to be 11.58, 11.30 and 11.57 kcal./mole, respectively, for 6, 8 and 10% reatcion, so that the average value of E is 11.48 ± 0.2 kcal./mole.

Iodine Bromide Catalysis.—The examination of the IBr-catalysis in the bromination of anisole in glacial acetic acid was carried out by conducting two sets of experiments. In the first set, the concentration of anisole and that of *total* bromine were kept constant at 0.04*M* and 0.018*M*, respectively, and the iodine concentration was progressively increased from 0 to 0.1*M*. In the second set, the concentration of anisole and that of *free* bromine were kept constant at 0.02*M* each, and the IBr concentration was increased from 0 to 0.06*M*.

Utilising the data obtained in the first set of experiments, the percentage of total bromine reacting in the first 15 seconds of the reaction was plotted against the ratio of the concentration of total iodine to total bromine, as shown in Fig. 3. From Fig. 3 it is seen that the rate of bromination is a maximum when the ratio of iodine to bromine is 0.35. Assuming that in glacial acetic acid the iodine added to bromine will be present wholly as IBr, calculation shows that at the catalytic maximum, the ratio of IBr to free bromine is 1.076, or approximately unity. In other words, one molecule of IBr must act as catalyst for each molecule of free bromine in the rate-determining step. Hence, in glacial acetic acid, the value of '*m*' in the rate-equation (1) is unity.

FIG. 3



The results of the second set of experiments are recorded in Table III from which it is evident that the percentage of free bromine reacting in the first 15 seconds increases steadily with increasing concentration of IBr. The plot of log k_2 against log [IBr] is linear, with a slope of 0.9, or nearly unity, thus confirming the value of 1 for '*m*' in the rate-equation (1).

TABLE III

Solvent: Glacial acetic acid. Temp. = 30°. Anisole = 0.02*M*.

Conc. of total Br.	Conc. of total I.	Conc. of free Br.	Conc. of IBr.	% Free Br consumed in 15 secs.	k_2.
0.01995*M*	0.0000*M*	0.01995*M*	0*M*	4.9	0.343
0.02105	0.0010	0.02005	0.0020	13.7	1.057
0.02206	0.0020	0.02006	0.0040	20.8	1.749
0.02402	0.0040	0.02002	0.0080	33.2	3.314
0.02650	0.0060	0.02050	0.0120	43.0	5.024
0.02834	0.0080	0.02034	0.0160	49.5	6.537
0.03083	0.0100	0.02083	0.0200	54.3	7.923
0.03371	0.0125	0.02120	0.0250	58.8	9.528
0.03669	0.0150	0.02170	0.0300	62.5	11.110
0.04024	0.0200	0.02024	0.0400	71.1	16.360
0.05087	0.0300	0.02087	0.0600	81.2	28.750

DISCUSSION

Mechanism in CCl_4.—The mechanism of the anisole-IBr reaction in CCl_4 is similar to that proposed earlier for the phenol-IBr reaction, except for the fact that the rate-determining step now involves two molecules of IBr as catalyst instead of one as in the case of phenol (*loc. cit.*).

$$2\ IBr \overset{K_1}{\rightleftharpoons} I_2 + Br_2 \quad \ldots \quad \ldots \quad (4)$$

$$C_6H_5.OCH_3 + Br_2 \overset{K_2}{\rightleftharpoons} C_6H_5.OCH_3, Br_2 \quad \ldots \quad \ldots \quad (5)$$

$$C_6H_5.OCH_3,Br_2 + 2IBr \xrightarrow[\text{slow}]{k} C_6H_5.\overset{+}{O}CH_3Br + (2\ IBr)\ Br^- \quad \ldots \quad (6)$$

$$C_6H_5.\overset{+}{O}CH_3Br \xrightarrow[\text{fast}]{} CH_3O\ C_6H_4Br + H^+ \quad \ldots \quad (7)$$

$$H^+ + (2\ IBr)Br^- \xrightarrow[\text{fast}]{} HBr + 2\ IBr \quad \ldots \quad \ldots \quad (8)$$

From equations (5) to (8), the rate of bromination is given by

$$d[CH_3O.C_6H_4Br]/dt = k.K_2\ [C_6H_5.OCH_3]\ [Br_2]\ [IBr]^2 \quad \ldots \quad (9)$$

in keeping with the experimental results presented in the section on IBr-catalysis.

Taking into account equation (4), in which bromine and iodine are produced in equal amounts from iodine bromide, the concentration of bromine is given by $[IBr]\sqrt{K_1}$. Insertion of this value for bromine in equation (9) leads to

$$d[CH_3O.C_6H_4Br]/dt = (k.K_2.\sqrt{K_1})\ [C_6H_5.OCH_3]\ [IBr]^3 \quad \ldots \quad (10)$$

which accounts for the overall kinetic order of four, 1 for anisole and 3 for iodine bromide.

That the rate-determining step (6) requires two molecules of IBr, and not one as in the case of phenol, needs explanation. The electron density at the *para* position will be greater for phenol than for anisole as a result of hyperconjugation, as evidenced by the mesomeric moments: phenol 1.12, anisole 0.4 (Remick, "Eelctronic Interpretation of Organic Chemistry", 1946, p. 88). Consequently, the binding between phenol and bromine in the charge-transfer molecular complex (C_6H_5OH,Br_2) will be stronger than that in the case of anisole. The Br—Br bond in the complex (C_6H_5OH,Br_2) will therefore be sufficiently polarised for one molecule of IBr to catalyse the removal of bromide ion as IBr_2^-. The weaker bond between anisole and bromine in ($C_6H_5.OCH_3,Br_2$) leaves the Br—Br bond fairly strong, and so two molecules of IBr are required to bring about the catalytic elimination of Br^- in the form of $(2\ IBr)Br^-$, as indicated in equation (6).

The anisole—IBr reaction has a negative temperature coefficient (E = -3.12 kcal./mole) throughout the range of -15.5° to 40°, unlike the phenol—IBr reaction (Yeddanapalli *et al.*, *loc. cit.*) which has a positive temperature coefficient between 0° and 10° (E = 3.44 kcal./mole) and a negative value between 30° and 40° (E = -18.46 kcal./mole), the inversion taking place at 19°. This inversion in the case of phenol

was explained on the basis of the dissociation of the phenol-bromine molecular complex at temperatures above 19°. Since the binding between anisole and bromine in the anisole-bromine molecular complex is weaker than that in the case of phenol, as explained above, it is reasonable to assume that the anisole-bromine complex begins to dissociate sensibly even at -15.5°. This accounts for the observed negative temperature coefficient throughout the range of -15.5° to 40° for the anisole—IBr reaction in CCl_4.

Modified Equation for explaining the Catalytic Maximum.—The equation derived by Tsuruta *et al.* (*loc. cit.*) to account for the catalytic maximum observed in aromatic brominations is

$$y/x = m/(m + 1) \quad \ldots \quad \ldots \quad \ldots \quad (11)$$

where 'x' and 'y' stand for the total molar concentration of bromine and iodine respectively. Since 'm' is 2 for the anisole—IBr reaction in CCl_4, the value of y/x at the catalytic maximum must be 0.66 according to the above equation. But the experimental value is only 0.49. In the bromination of benzene (without any solvent) and of mesitylene in CCl_4 with 'm' = to 3 and 2 respectively, the catalytic maximum occurred at 0.61 and 0.51 (Robertson *et al.*, *J. Chem. Soc.*, 1949, 933 ; Blake and Keefer, *J. Amer. Chem. Soc.*, 1955, **77**, 3707), contrary to the values of 0.75 and 0.66 deduced from Tsuruta's equation.

It has been pointed out recently (Gnanapragasam and Yeddanapalli, *Curr. Sci.*, 1957, **26**, 47) that a modification of Tsuruta's equation to

$$y/x = m/(m + 2) \quad \ldots \quad \ldots \quad \ldots \quad (12)$$

leads to a better agreement between the calculated and experimental values of y/x at the catalytic maximum. According to this modified equation, the values of y/x at the catalytic maximum should be 0.60, 0.50 and 0.33 corresponding to the 'm' values of 3, 2 and 1. The experimentally determined values for y/x are in close agreement with these, viz., 0.61 for benzene with 'm' equal to 3, 0.51 and 0.49 for mesitylene and anisole, respectively, for which 'm' is 2, and 0.30 for phenol with 'm' = 1.

Now, equation (12) can be deduced from a consideration of the amounts of free bromine and IBr, which play a decisive role in the bromination reactions. We have shown that in the bromination of anisole in CCl_4, the catalytic maximum occurs when the ratio of IBr to free bromine is 1.9, or nearly 2. Since in this reaction 'm' has also been established to be 2, we arrive at the conclusion that at the catalytic maximum

$$(\text{IBr/free bromine}) = m \quad \ldots \quad \ldots \quad (13)$$

If 'x' and 'y' are the initial concentration of bromine and iodine respectively, 'x' being always in excess of 'y', then the concentrations of iodine bromide and free bromine are $2y$ and $(x\text{-}y)$, respectively. Substituting these values in equation (13), we get

$$2y/(x\text{-}y) = m \quad \ldots \quad \ldots \quad \ldots \quad (14)$$

which on rearrangement leads to equation (12).

The occurrence of a catalytic maximum in the so-called iodine-catalysed brominations is due to the fact that the catalyst IBr is formed in the reaction medium by taking a part of the bromine, which is itself a reactant. Hence, iodine increases the rate of bromination, if added in small amounts, by producing the catalyst, IBr ; but if present in excess, it acts as an inhibitor by decreasing the concentration of free bromine, which is the effective brominating agent.

Mechanism in Glacial Acetic Acid.—The mechanism of the anisole—IBr reaction in CCl_4 cannot be applied for the same reaction in glacial acetic acid, because spectroscopic measurements have shown that 1 : 1 molecular complexes of aromatic compounds with bromine and iodine are not formed in the latter solvent (cf. this *issue*, p. 745). There is evidence, on the other hand, to show that bromine forms charge-transfer complexes with acetic acid molecules. However, the mechanism suggested earlier for the phenol—IBr reaction in glacial acetic acid can be applied to the anisole—IBr reaction also, in view of the close similarity in the kinetics and energetics of the two reactions. Both are of the third order, first with respect to the aromatic compound and second for IBr. The catalytic maximum for phenol occurs at 0.31 for y/x and for anisole at 0.35. Further, in the case of anisole, the value of unity for 'm' has been established by an independent method (*vide supra*).

The observed activation energy for the anisole—IBr reaction (11.48 kcal./mole) is about 2 kcal. greater than that for the phenol—IBr reaction (9.72 kcal./mole), although the mechanisms for both the reactions are similar. This must be due to the result of the lower reactivity of anisole in bromination, compared to phenol: the time required for 10% reaction with IBr at 30° is 50 seconds for phenol, and 3720 seconds for anisole.

The catalytic maximum observed in the bromination of phenol and anisole in glacial acetic acid cannot be explained on the basis of Tsuruta's equation (11), because it has been derived on the assumption of a mechanism involving 1 : 1 molecular complex between the aromatic compound and bromine, but spectrophotometric data have been presented (cf. this *issue*, p. 745) to show that such complexes do not exist in acetic acid medium. Our modified equation (12) is applicable to reactions in glacial acetic acid also, since it has been deduced only from a consideration of free bromine and iodine bromide, without invoking any molecular complex. For phenol and anisole, 'm' is equal to unity, so that y/x at the catalytic maximum according to the modified equation (12) must be 0.33, in good agreement with the observed values of 0.31 and 0.35, respectively. This provides further evidence for the validity of the proposed equation for explaining the catalytic maximum in aromatic brominations.

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STUDIES IN THE FRIES MIGRATION. PART XV. THE FRIES ISOMERISATION OF CHLOROPHENYL ACETATES

By N. M. Shah and S. R. Parikh

The Fries reaction of three isomeric chlorophenyl acetates has been systematically investigated.

Shah *et al.* in earlier parts of this series (this *Journal*, 1946, **23**, 199, 234 ; 1949, **26**, 235 ; 1950, **27**, 531 ; 1956, **33**, 318 et seq) have investigated the Fries isomerisation of diversely substituted phenolic esters. As very little systematic work in this respect appears to have been done on halogenated phenolic esters, the present work has been undertaken with *o*-, *m*- and *p*-chlorophenyl acetates. *o*-Chlorophenyl acetate has been studied under a variety of conditions. The results are presented in Table I.

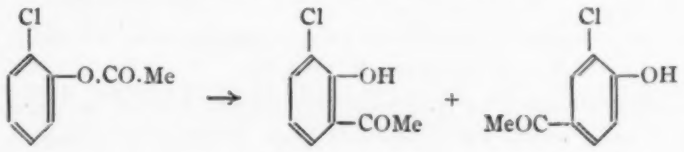
TABLE I

No.	Temp.	$AlCl_3$.	Solvent.	Weight of pure hydroxy acetophenones. *2-Hydroxy-3-chloro-.	*4-Hydroxy 3-chloro-.
			A. *o*-Chlorophenyl acetate.		
1.	150°	3.3 *M*	Nil	10 g. from 30 g. acetate	7 g. from 30 g. acetate
2.	200°	3.3	,,	Do	Do
3.	150°	1.5	,,	,,	,,
4.	200°	1.5	,,	,,	,,
5.	150°	1.5	Nitrobenzene	No product	**
6.	100°	1.5	,,	1 g. from 10 g. acetate	3 g. from 10 g. acetate
7.	Room temp. (25-30°)	1.5	,,	Do	2 g. from 10 g. acetate
8.	Do	1.5	Acetylene tetrachloride	Traces	1 g.
9.	Do	1.5	,,	No product	No product
			B. *m*-Chlorophenyl acetate	(III).	(IV).
1.	150°	1.5	Nil	6 g. from 10 g. acetate	Traces
2.	Room temp.	,,	,,	5 g. from 10 g acetate	0.5 g.
3.	Ice-bath (0°)	,,	,,	Do	0.5

*Wt. mentioned is for the pure product after crystallisation.
**The product was obtained in charred condition.

In all cases similar results were obtained. Two migration products were formed, which were separated by steam distillation. The migration products have been assigned the constitution, 2-hydroxy-3-chloro-(I) and 4-hydroxy-3-chloro-acetophenone (II) respectively, as (I) develops a red colour with alcoholic ferric chloride, it affords methoxy and semicarbazone derivatives, and its methoxy ether on oxidation gives rise to 2-methoxy-3-chlorobenzoic acid ; whereas (II) does not respond to ferric colour reaction, but furnishes methoxy and semicarbazone derivatives ; its methoxy ether on oxidation gives rise to 4-methoxy-3 chlorobenzoic acid (Schall and Dralle, *Ber.*, 1884,

17, 2529), and further, (II) agrees with the ketone obtained by the Friedel-Crafts acetylation of *o*-chlorophenol (Nencki and Stober, *Ber.*, 1897 **30**, 1771).



(I) (II)

Similarly, the Fries isomerisation of *p*-chlorophenyl acetate was investigated; only one product, 2-hydroxy-5-chloroacetophenone, was obtained in excellent yield, identical with the Friedel-Crafts acetylation product of *p*-chlorophenol (Nencki and Stober, *loc. cit.*).

Sen and Tiwari (this *Journal*, 1952, **29**, 419) carried out the Fries migration of *m*-chlorophenyl acetate and reported only one product, to which they assigned the constitution, 2-hydroxy-4-chloroacetophenone (III). We have investigated this migration under different conditions (Table IB). In all cases, two isomeric ketones have been obtained. 2-Hydroxy-4-chloroacetophenone (III) is the main product, always accompanied with the isomeric 4-hydroxy-2-chloroacetophenone (IV) in small quantity.

It is evident from the results that chlorine as a nuclear substituent in phenol does not hinder the migration. It is quite facile and takes place in both the vacant *ortho* and *para* positions in agreement with the behaviour of other phenolic esters.

EXPERIMENTAL

Fries Rearrangement of o-Chlorophenyl Acetate : Formation of 2-Hydroxy-3-chloro- and 4-Hydroxy-3-chloro-acetophenones

(*a*). *Without solvent*.—*o*-Chlorophenyl acetate (30 g.) was intimately mixed with anhydrous $AlCl_3$ (76 g., 3·3 *M*) in a flask fitted with an air condenser with $CaCl_2$ guard-tube. It was heated to 150° for 2 hours, cooled, decomposed with ice and HCl (5 c.c.) and subjected to steam distillation. The distillate on cooling furnished needles, m.p. 55°, yield 10 g. (Found : Cl, 20.64. $C_8H_7O_2Cl$ requires Cl, 20.82%). It develops a red colour with $FeCl_3$ and dissolves in alkali with a yellow colour.

The non-volatile residue in the flask was collected and crystallised from boiling water in long white needles, m.p. 96°, yield 7 g., agreeing with 3-chloro-4-hydroxy-acetophenone.

(*b*). *With solvent*.—The ester (10 g.) was added to a solution of anhydrous $AlCl_3$ (12.0 g., 1·5 *M*) in dry nitrobenzene (25 c.c.) and heated to 100° as before. It was then worked up as before and steam-distilled, when the volatile component was obtained as an oil. It was extracted several times with NaOH and the alkaline extract acidified, when a white solid was obtained which was crystallised, m.p. 55°, yield 1 g.

The non-volatile product was collected and crystallised from boiling water, m.p. 96°, yield 3 g. It was identified as 3-chloro-4-hydroxyacetophenone by mixed m.p. with an authentic sample.

The *methoxy* derivative of 2-hydroxy-3-chloroacetophenone, prepared by acetone-K_2CO_3-dimethyl sulphate, separated as a liquid, b.p. 258°. (Found : Cl, 19.2. $C_8H_9O_2Cl$ requires Cl, 19.24%).

The *semicarbazone* of the same ketone was crystallised from hot water, m.p. 215°. (Found : N, 17.14. $C_9H_8O_2N_3Cl$ requires N, 17.39%).

The *methoxy* derivative of 4-hydroxy-3-chloroacetophenone, prepared as before, separated as a solid which was crystallised from hot water in granules, m.p. 80°. (Found : Cl, 19.15. $C_8H_9O_2Cl$ requires Cl, 19.24%).

The *semicarbazone* of the same ketone crystallised from hot water in granules, m.p. 210°. (Found : N, 17.17. $C_9H_8O_2N_3Cl$ requires N, 17.39%).

2-Methoxy-3-chlorobenzoic Acid.—To 2-methoxy-3-chloroacetophenone (1 g.) in NaOH (3 c.c., 20%), $KMnO_4$ (3 g.) was added in small quantities till decolorised and heated for nearly 6 hours. It was filtered and the filtrate acidified, when a white solid was obtained ; it was crystallised from alcohol, m.p. 215°. (Found : Cl, 18.92 ; equiv., 187.1 $C_8H_7O_2Cl$ requires Cl, 19.04% ; equiv., 186.5).

Fries Rearrangement of m-*Chlorophenyl Acetate : Formation of 4-Chloro-2-hydroxy- and 4-Hydroxy-2-chloro-acetophenones*

m-Chlorophenyl acetate (10 g.) was intimately mixed with anhydrous $AlCl_3$ (12 g., 1.5 *M*) and heated at 150° for 2 hours ($CaCl_2$ guard-tube). The reaction mixture was worked up as before. On steam distillation, an oil was obtained, identical with 4-chloro-2-hydroxyacetophenone of Sen and Tiwari (*loc. cit.*), yield 6 g. The non-volatile brown mass was collected and crystallised from boiling water in white needles, m.p. 110°. (Found : Cl, 20.72. Calc. for $C_8H_7O_2Cl$: Cl, 20.82%). It does not show any colour with ferric chloride.

The *semicarbazone* of 4-hydroxy-2-chloroacetophenone separated as long needles, m.p. 187°. (Found : N, 17.14. $C_9H_8O_2N_3Cl$ requires N, 17 39%).

Fries Rearrangement of p-*Chlorophenyl Acetate : Formation of 5-Chloro-2-hydroxyacetophenone*

p-Chlorophenyl acetate (10 g.) and anhydrous $AlCl_3$ (76 g., 3.3 *M*) were heated at 160° for 2 hours and then worked up as before. The product was collected and crystallised from boiling water in long needles, m.p. 56-57°, yield 10 g. It was found identical with 5-chloro-2-hydroxyacetophenone (Nencki and Stober, *loc. cit.*).

Similar results were obtained when the reaction was repeated at 200° with 1.5 moles of anhydrous $AlCl_3$.

The migration was repeated (*i*) at room temperature and (*ii*) at 150-60° with $AlCl_3$ (1.5 *M*) using acetylene tetrachloride as solvent. No ketonic product could be obtained. With nitrobenzene as solvent, a low yield of the ketone was obtained.

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SEARCH FOR NEW ANTIMALARIALS. PART III. SYNTHESIS OF SOME SUBSTITUTED QUINAZOLINES

By A. B. Sen and P. R. Singh

Twentyfour substituted 4 alkylamino- and 4-dialkylamino-quinazolines have been synthesised as possible antimalarials.

The similarity of quinazoline to quinoline, the apparent lower toxicity of its derivatives as compared to those of quinoline (Valenti, *Biochim terap. Sper.*, 1930, **17**, 84), the occurrence of the quinazoline nucleus in the antimalarial alkaloids, febrifugine and *iso*febrifugine (Asahina, *J. Chem. Soc.*, 1927, 1708), and the usefulness of quinazoline derivatives as valuable chemotherapeutic agents (Paal *et al.*, *Ber.*, 1889, **22**, 2683 ; Gabriel *et al.*, *Chem. Zentrl.*, 1905, **76**, 182 ; 1931, **102**, 87 ; *Chem. Abst.*, 1931, **25**, 4664 ; Farbenind, *ibid.*, 1929, **23**, 396 ; *Chem. Zentrl.*, 1930, **101**, 1773) had led to the synthesis of a large number of quinazoline derivatives as potential antimalarial drugs (Magidson *et al.*, *J. Gen. Chem. U.S.S.R.*, 1938, **8**, 1797 ; Smith *et al.*, *J. Amer. Chem. Soc.*, 1946, **68**, 1301 ; Price *et al.*, *ibid.*, 1946, **68**, 1305 ; Endicott *et. al.*, *ibid.*, 1946, **68**, 1299, 1303 ; Christensen *et al.*, *ibid.*, 1946, **68**, 1306 ; Curd *et al.*, *J. Chem. Soc.*, 1947, 775 ; 1948, 1759 ; Chapman *et al.*, *ibid.*, 1947, 891 ; Elderfield *et al.*, *J. Org. Chem.*, 1947, **12**, 405 ; Shakti Rani *et al.*, this *Journal*, 1953, **30**, 331), most of which have displayed marked physiological activity (Valenti, *loc. cit.*).

The present work reports the synthesis of twentyfour halogen-substituted quinazolines (III) having an ethanolamino or a diethanolamino side chain at position-4, which have been synthesised, starting from different anthranilic acids.

Mono- and dihalogenoanthranilic acids have been prepared by the direct halogenation of anthranilic acid. Six mixed anthranilic acids (3-Br-5-Cl ; 3-I-5-Cl ; 3-Cl-5-Br ; 3-I-5-Br ; 3-Cl-5-I and 3-Br-5-I) have been prepared for the first time by the halogenation of anthranilic acid in two steps. In each case, the 5-substituted acid was obtained first, further halogenation leading to a 3 : 5-dihalogeno-anthranilic acid.

Anthranilic acids on condensation with formaide yielded the corresponding 4-hydroxyquinazolines (I) (Endicott *et al.*, *loc. cit.*), which on heating with phosphorus pentachloride and phosphorus oxychloride were converted into 4-chloroquinazolines (II). The latter on condensation with ethanolamine or diethanolamine afforded the required quinazoline derivative (Chapman *et al.*, *loc. cit.*).

Quinazolines, thus prepared, have been sent to the Malaria Institute of India, Delhi, for the evaluation of their antimalarial activity.

EXPERIMENTAL

Substituted Anthranilic Acids.—Six halogenated anthranilic acids, viz., 5-chloro- (Endicott *et al.*, *J. Amer. Chem. Soc.*, 1946, **68**, 1303); 5-bromo- (Wheeler *et al.*, *ibid.*, 1910, **32**, 770); 5-iodo- (Organic Syntheses Coll. Vol. 2, 1943, p. 349); 3:5-dichloro-(Atkinson *et al.*, *Chem. Abst.*, 1952, **46**, 951 [d]); 3:5-dibromo- (Wheeler *et al.*, *loc. cit.*) and 3:5-di-iodo- (Wheeler *et al.*, *Amer. Chem. J.*, 1921, **43**, 405) were prepared by the direct halogenation of anthranilic acid.

3-Bromo-5-chloroanthranilic Acid.—To 5-chloroanthranilic acid (0.1*M*, 17.2 g.), dissolved in hot glacial acetic acid (100 c.c.), bromine (2.8 c.c.) in glacial acetic acid (10 c.c.) was added with stirring. After cooling, the crystals separated, which were filtered, washed with cold acetic acid and then with benzene, pressed and dried. On recrystallisation from hot alcohol, white needles were obtained in 74% yield, m.p. 227-29°. (Found: Neut. equiv., 249.9; N, 5.53. $C_7H_5O_2NClBr$ requires neut. equiv., 250.5; N, 5.59%)

3-Iodo-5-chloroanthranilic Acid.—To a boiling solution of 5-chloroanthranilic acid (0.1 *M*, 17.2 g.) in glacial acetic acid (100 c.c.) iodine monochloride (0.11 *M*) in glacial acetic acid (10 c.c.) was added dropwise with continuous stirring. The mixture was stirred for one hour on the boiling water-bath. The crystals separating on cooling were filtered, washed with cold acetic acid and recrystallised from hot alcohol in light brown needles, m.p. 246-47°, yield 71%. (Found: Neut. equiv., 296.7; N, 4.66. $C_7H_5O_2NClI$ requires neut. equiv., 297.5; N, 4.71%).

3-Chloro-5-bromoanthranilic Acid.—Chlorine was passed into a methanolic solution (60 c.c.) of 5-bromoanthranilic acid (0.1*M*, 21.6 g.) at room temperature till the total weight increased by 3.5 g. Methanol was distilled off and the residual 3-chloro-5-bromoanthranilic acid crystallised from acetic acid. On further recrystallisation from hot alcohol, colorless needles of m.p. 210-11° were obtained in 79% yield. (Found: Neut. equiv., 249.8; N, 5.56. $C_7H_5O_2NClBr$ requires neut. equiv., 250.5; N, 5.59%).

3-Iodo-5-bromoanthranilic Acid.—5-Bromoanthranilic acid (0.1*M*, 21.6 g.) in glacial acetic acid solution (100 c.c.) was iodinated with iodine monochloride (0.11*M*) by the method described above. Recrystallisation of the crude product from hot alcohol furnished light tan-coloured flat needles, m.p. 222-23°, yield 73%. (Found: Neut. equiv., 341.8; N, 5.82. $C_7H_5O_2NClI$ requires neut. equiv., 297.2; N, 5.79%).

3-Chloro-5-iodoanthranilic Acid.—5-Iodoanthranilic acid (0.1*M*, 26.3 g.) in methanolic solution (60 c.c.) was chlorinated as described above. On recrystallisation of the crude product from hot acetic acid, light brown needles were obtained, m.p. 230-32°, yield 63%. (Found: Neut. equiv., 297.2; N, 4.70. $C_7H_5O_2NClI$ requires neut. equiv., 297.5; N, 4.71%).

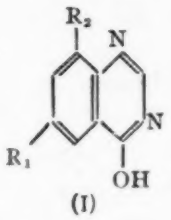
3-Bromo-5-iodoanthranilic Acid.—5-Iodoanthranilic acid (0.1*M*, 26.3 g.) was brominated with bromine (2.8 c.c.) in acetic acid solution by a similar method, as described above. On recrystallisation from hot alcohol, colorless needles were obtained, m.p. 227-28°, yield 78%. (Found: Neut. equiv., 341.5; N, 5.81. $C_7H_5O_2NBrI$ requires neut. equiv., 342.0; N, 5.79%).

4 *Hydroxyquinazolines* were prepared according to the method described by Endicott *et al.* (*loc.cit.*). A mixture of the substituted anthranilic acid (0.1*M*) and formamide (0.4*M*) was heated in an oil-bath using a bulb-condenser at 135-40° for 1-1½ hours and then for another 15-30 minutes at a higher temperature (140-80°). Crystals separating on cooling were filtered, washed with a little 0.2*N*-NaOH (aq.) and then with water and recrystallised from hot 95% ethanol.

Crystalline picrates of 4-hydroxyquinazolines were obtained by mixing hot saturated alcoholic solutions of 4-hydroxyquinazoline and picric acid.

The 4-hydroxyquinazolines prepared and their picrates are recorded in Table I.

TABLE I



(I)

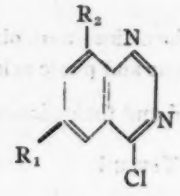
	4-Hydroxyquinazolines.						Picrates.			
	Substitution				% Nitrogen.				% Nitrogen.	
No.	R_1.	R_2.	M.P.	Yield.	Found.	Calc.	M.P.	Formula.	Found.	Calc.
1	Cl	H	262-63°	91%	15.43	15.51	201°	$C_{14}H_8O_8N_5Cl$	16.93	17.10
2	Cl	Cl	327°	95	12.99	13.03	261-63°	$C_{14}H_7O_8N_5Cl_2$	15.77	15.76
3	Br	H	271°	89	12.38	12.45	209-11°	$C_{14}H_8O_8N_5Br$	15.13	15.42
4	Br	Br	279°	86	9.17	9.21	208°	$C_{14}H_7O_8N_5Br_2$	13.10	13.13
5	I	H	281°	90	10.33	10.30	217-18°	$C_{14}H_8O_8N_5I$	13.86	13.97
6	I	I	287° (d)	91	6.95	7.04	229°	$C_{14}H_7O_8N_5I_2$	10.98	11.17
7	Cl	Br	341° (d)	87	10.77	10.79	271°	$C_{14}H_7O_8N_5ClBr$	14.21	14.33
8	Cl	I	301-302° (d)	87	9.15	9.14	244°	$C_{14}H_7O_8N_5ClI$	13.12	13.07
9	Br	Cl	336° (d)	91	10.81	10.79	264°	$C_{14}H_7O_8N_5ClBr$	14.19	14.33
10	Br	I	329° (d)	92	7.89	7.98	237-39°	$C_{14}H_7O_8N_5BrI$	12.06	12.07
11	I	Cl	309-10° (d)	89	9.12	9.14	222-23°	$C_{14}H_7O_8N_5ClI$	12.95	13.07
12	I	Br	316-17° (d)	91	8.04	7.98	231-33°	$C_{14}H_7O_8N_5BrI$	11.92	12.07

4-*Chloroquinazolines* (cf. Norman *et al.*, *loc.cit.*; Endicott *et al.*, *loc.cit.*).—4-Hydroxyquinazoline (0.1*M*) was refluxed with a mixture of PCl_5 (0.1*M*) and redistilled $POCl_3$ (35-40 c.c.) at 115-20° till the mixture became homogeneous and substantially clear (1-2 hours.). The excess of $POCl_3$ was distilled off under reduced pressure. The residue was extracted with chloroform ether, benzene or petroleum ether (range 80-100°) after the addition of ice and a small amount of saturated sodium carbonate solution to it. The residue from the dried extract was pure 4-chloroquinazoline derivative.

Picrates of the 4-chloroquinazolines were easily prepared in absolute alcohol by the usual method.

These 4-chloroquinazolines and their picrates are recorded in Table II.

TABLE II



(II)

4-Chloroquinazolines.						Picrates.			
				% Nitrogen.				% Nitrogen.	
No.*	M.P.	Yield.	Extraction.	Found.	Calc.	M.P.	Formula.	Found.	Calc.
1	154-55°	90%	Chloroform	14.12	14.07	173°	$C_{14}H_7O_7N_6Cl_2$	16.31	16.36
2	236-37°	87	Chloroform	11.96	11.99	221-23°	$C_{14}H_6O_7N_6Cl_3$	15.24	15.14
3	178°	62	Ether	11.44	11.50	189-90°	$C_{14}H_7O_7N_6ClBr$	14.77	14.81
4	189-90°	67	Chloroform	8.59	8.68	212°	$C_{14}H_6O_7N_6ClBr_2$	12.58	12.69
5	193-95°	71	Petroleum ether	9.63	9.64	201-202°	$C_{14}H_7O_7N_6Cl\ I$	13.41	13.47
6	242-43°	63	Benzene	6.68	6.72	217-18°	$C_{14}H_6O_7N_6Cl\ I_2$	10.78	10.84
7	239-40°	59	Chloroform	10.01	10.08	209-11°	$C_{14}H_6O_7N_6Cl_2Br$	13.80	13.81
8	225-27°	56	Petroleum ether	8.60	8.62	197°	$C_{14}H_6O_7N_6Cl_2I$	12.55	12.64
9	231-32°	61	Chloroform	10.11	10.08	200-201°	$C_{14}H_6O_7N_6Cl_2Br$	13.77	13.81
10	216-17°	70	Chloroform	7.55	7.58	225°	$C_{14}H_6O_7N_6ClBrI$	11.57	11.69
11	211°	80	Petroleum ether	8.56	8.62	221°	$C_{14}H_6O_7N_6Cl_2I$	12.58	12.64
12	222-23°	73	Chloroform	7.57	7.58	211-13°	$C_{14}H_6O_7N_6ClBrI$	11.71	11.69

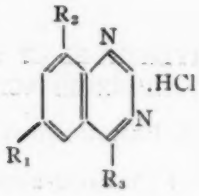
* Corresponding numbers indicate the substituents R_1 & R_2 as in Table I.

4-Alkyl- and Dialkyl-aminoquinazolines (cf. Chapman *et al., loc.cit.*).—The appropriate 4-chloroquinazoline (0.1*M*) and mono- or di-ethanolamine (0.11*M*) in alcohol (65-70 c.c.) or alcohol-benzene (1:1, 65-70 c.c.) containing 2 drops of HCl (conc.) were refluxed on a water-bath for 3½ – 4 hrs. The crystalline 4-alkylaminoquinazoline monohydrochloride was occasionally deposited during the initial refluxing and was isolated by the direct addition of ether to the cold reaction mixture, and recrystallised from hot absolute alcohol.

The crystalline picrates of the alkyl- and dialkyl-aminoquinazolines were obtained easily on mixing together the hot saturated solutions of picric acid and the particular base-hydrochloride in absolute alcohol.

The results of analysis and melting points etc. of the 4-alkyl- and dialkylaminoquinazoline hydrochlorides and the picrates, thus prepared, are recorded in Table III.

TABLE III



(III)

No.	Substitution. R_1	Substitution. R_2	M.P.	Yield.	% Nitrogen. Found:	Calc.	Picrates. M.P.	Formula.	% Nitrogen. Found	Calc
					$R_3 = -NH.CH_2CH_2OH$.					
1	Cl	H	207-209°	88%	16.04	16.15	197 98°	$C_{16}H_{13}O_8N_6Cl$	18.55	18.57
2	Cl	Cl	219-20°	79	14.10	14.26	176-77°	$C_{16}H_{12}O_8N_6Cl_2$	17.18	17.25
3	Br	H	214°	81	13.57	13 79	168°	$C_{16}H_{13}O_8N_6Br$	16.90	16.92
4	Br	Br	223°	72	10.88	10 84	182-83°	$C_{16}H_{12}O_8N_6Br_2$	14.53	14 58
5	I	H	226-27°	69	11.84	11.15	166-67°	$C_{16}H_{13}O_8N_6I$	15.41	15.44
6	I	I	239-41°	61	8 68	8.80	170-71°	$C_{16}H_{12}O_8N_6I_2$	12.50	12.54
7	Cl	Br	219°	65	12.42	12.39	162°	$C_{16}H_{12}O_8N_6ClBr$	15.75	15.81
8	Cl	I	228°	76	10.80	10.88	177°	$C_{16}H_{12}O_8N_6ClI$	14.48	14.52
9	Br	Cl	230-31°	74	12.31	12.39	196-97°	$C_{16}H_{12}O_8N_6ClBr$	15.86	15 81
10	Br	I	235°	85	9 77	9 76	205-206°	$C_{16}H_{12}O_8N_6BrI$	13.50	13 48
11	I	Cl	227-28°	80	10.79	10.88	201-203°	$C_{16}H_{12}O_8N_6ClI$	14.49	14 52
12	I	Br	234-35°	76	9.68	9.76	191-92°	$C_{16}H_{12}O_8N_6BrI$	13.44	13 48
					$R_3 = -N(CH_2.CH_2OH)_2$.					
13	Cl	H	211-12°	83	13.77	13.81	180°	$C_{18}H_{17}O_9N_6Cl$	16 89	16.95
14	Cl	Cl	222-23°	80	12.39	12.41	169°	$C_{18}H_{16}O_9N_6Br$	15 77	15.82
15	Br	H	219°	76	11.96	12.05	161°	$C_{18}H_{17}O_9N_6Br$	15.48	15.53
16	Br	Br	225-27°	75	9.79	9.83	201-203°	$C_{18}H_{16}O_9N_6Br_2$	13.46	13.55
17	I	H	231°	73	10.55	10.62	204°	$C_{18}H_{17}O_9N_6I$	14.27	14.29
18	I	I	251-53°	60	7.99	8.06	211-13°	$C_{18}H_{16}O_9N_6I_2$	11.79	11.76
19	Cl	Br	225-26°	70	10 83	10 84	199°	$C_{18}H_{16}O_9N_6ClBr$	14.61	14.59
20	Cl	I	224°	68	9.75	9.77	188-89°	$C_{18}H_{16}O_9N_6ClI$	13.47	13.50
21	Br	Cl	237-38°	66	10.81	10.84	203°	$C_{18}H_{16}O_9N_6ClBr$	14.63	14.59
22	Br	I	240°	71	8 88	8 85	209 210°	$C_{18}H_{16}O_9N_6BrI$	12.55	12.60
23	I	Cl	233-34°	64	9.79	9.77	186-87°	$C_{18}H_{16}O_9N_6ClI$	13.46	13.50
24	I	Br	239-41°	63	8.78	8.85	195-96°	$C_{18}H_{16}O_9N_6BrI$	12 59	12.60

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BROMINATION OF ARYLAMIDES OF 2-HYDROXY-4-METHOXY-BENZOIC ACID

By D. M. Phatak and G. V. Jadhav*

Bromination of some arylamides of 2-hydroxy-4-methoxybenzoic acid has been effected under different conditions and the constitution of the bromo derivatives determined.

It has been observed that methylation of the hydroxy group of 2-hydroxybenzoic acid completely deactivates the acidic nucleus towards chlorination, as in the case of arylamides (Hirwe, Jadhav and Sukhtankar, this *Journal*, 1939, **26**, 281). Similar deactivating effect has also been observed by the present authors in the case of bromination of arylamides of 4-methoxybenzoic acid (*ibid.*, 1959, **36**, 221).

In the present work, bromination of arylamides of 2-hydroxy-4-methoxybenzoic acid has been carried out with a view to studying the effect of the introduction of hydroxy group in 4-methoxybenzoic acid on the reactivity of the arylamides during bromination.

Bromination in acetic acid medium with one or two moles affords monobromo derivatives in the case of anilide, *p*-toluidide, *o*- and *m*-nitroanilides and *p*-anisidide. With more bromine solution, anilide, *m*-toluidide, *β*-naphthylamide and *m*-nitroanilide dibromo derivatives are obtained.

The dibromo derivative of *m*-nitroanilide is found identical with the one obtained by the action of liquid bromine on *m*-nitroanilide.

With liquid bromine, anilide, *m*- and *p*-toluidides, *o*- and *p*-anisidides and *p*-phenetidide furnished tetrabromo derivatives, whereas *o*- and *p*-nitroanilides afforded tribromo derivatives, and *m*-nitroanilide yielded dibromo derivative.

The constitution of these bromo derivatives has been arrived at by their hydrolysis with alcoholic caustic potash solution or 80% (v / v) sulphuric acid. In the case of alkaline hydrolysis of the compounds marked* and *† (in the table), both acidic and basic components have been isolated, whereas in the acid hydrolysis of *β*-naphthylamide derivative, only the basic component has been separated. The acid might have undergone sulphonation under the experimental conditions. These components have been identified by mixed melting points with authentic specimens.

In the case of compounds marked † (in the table) the constitution has been confirmed by synthesis from the requisite acid and the amine in presence of phophorus trichloride and heating the mixture on a boiling water-bath for about 4 hours.

In the case of monobromo and dibromo derivatives, the acidic component is always only 2-hydroxy-4-methoxy 5-bromobenzoic acid, excepting in the case of the dibromo derivative of *m*-nitroanilide, where the acidic component is 2-hydroxy-4-methoxy-3 : 5-dibromobenzoic acid. In the case of higher bromo derivatives, the acid is always 2-hydroxy-4-methoxy-3 : 5-dibromobenzoic acid.

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TABLE I

"C" represents 2-hydroxy-4-methoxybenz-

"C-5-B" represents 2-hydroxy-4-methoxy-5-bromoben-

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TABLE I

"C" represents 2-hydroxy-4-methoxybenz-. "C-5-B" represents 2-hydroxy-4-methyxy-5-bromobenz-.

Arylamide.	30% Br soln. added.	Bromo derivative.	Cryst. from.	Cryst. shape.	M.P.	Formula.	%Bromine. Found.	%Bromine. Calc.
C-anilide.	4·4 c.c.	C-5-B-anilide †	EtOH (dil)	Colorless needles	211-12°	$C_{14}H_{12}O_3NBr$	25.0	24.8
Do	6.6	C-5-B-4′-bromoanilide†	AcOH (dil.)	Do	243-44°	$C_{14}H_{11}O_3NBr$	39.5	39.9
C-*m*-toluidide	6.3	C-5-B-4′-bromo-*m*-toluidide *	AcOH	,,	258-59°	$C_{15}H_{13}O_3NBr_2$	38.2	38.6
C-*p*-toluidide	4.2	C-5-B-*p*-toluidide †	EtOH (dil.)	,,	211-12°	$C_{15}H_{14}O_3NBr$	24.1	23.8
C-*p*-nitroanilide	3.6	C-5-B-*o*-nitroanilide *†	Benzene	Yellow needles	223-24°	$C_{14}H_{11}O_5N_2Br$	22.0	21.8
C-*m*-nitroanilide	3.6	C-5-B-*m*-nitroanilide *†	Acetic acid	Pale yellow needles	218-19°	$C_{14}H_{11}O_5N_2Br$	21.9	21.8
C-*p*-anisidide	3.9	C-5-B-*p*-anisidide †	,,	Colorless rectangular plates	200-201°	$C_{15}H_{14}O_4NBr$	23.1	22 7
C-*β*-naphthylamide	5.4	C-5-B-*α*-bromo-*β*-naphthylamide	,,	Colorless needles	221-22°	$C_{13}H_{13}O_3NBr_2$	35.9	35.5

TABLE II

"C" represents 2-hydroxy-4-methoxybenz-. "C-3 : 5-DB" represents 2-hydroxy-4-methoxy-3 : 5-dibromobenz-.

Arylamide.	Bromo derivative.	Cryst. from.	Cryst. shape.	M. P.	Formula.	%Bromine. Found.	%Bromine. Calc.
C-anilide	C-3 :5-DB-2′ :4′-dibromo-anilide*†	Acetic acid	Colorless needles	199-200°	$C_{14}H_9O_3NBr_4$	57.0	57.2
C-*m*-toluidide	C-3 :5-DB-4′ :6′-dibromo-*m*-toluidide *	Benzene	Do	184-85°	$C_{15}H_{11}O_3NBr_4$	55.5	55.8
C-*p*-toluidide	C-3 :5-DB-2′ :5′- (or 3′ :6′)-dibromo-*p*-toluidide*	Alcohol	Do	211-12°	$C_{15}H_{11}O_3NBr_4$	55.4	55.8
C-*o*-nitroanilide	C-3 :5-DB-2′-nitro-4′-bromoanilide*†	Do	Yellow needles	200-201°	$C_{14}H_9O_5N_2Br_3$	45.6	45.7
β-C-*m*-nitroanilide	C-3 :5-DB-*m*-nitroanilide*†	Acetic acid	Pale yellow needles	193-94°	$C_{14}H_{10}O_5N_2Br_2$	36.1	35.9
α-C-*p*-nitroanilide	C-3 :5-DB-2′-bromo-4′-nitroanilide*†	Do	Prismatic needles	230-31°	$C_{14}H_9O_5N_2Br_3$	45.9	45.7
C-*o*-anisidide	C-3 :5-DB-5′ :6′-dibromo-*o*-anisidide*	,,	Pink lustrous needles	222-23°	$C_{15}H_{11}O_4NBr_4$	54.4	54.3
C-*p*-anisidide	C-3 :5-DB-2′- :5′- (or 3′ :6′)-dibromo-*p*-anisidide *	,,	Colorless needles	250-51°	$C_{15}H_{11}O_4NBr_4$	54.4	54.3
C-*p*-phenetidide	C-3 :5-DB-2′ :5′- (or 3′ :6′-dibromo-*p*-phenetidide *	,,	Do	205-206°	$C_{16}H_{13}O_4NBr_4$	53.1	53.0

β: Bromination with four molecules of bromine in acetic acid affords the same product.
α: The reaction mixture is heated on a boiling water-bath for three hours and then left overnight at room temperature.

It thus shows that the introduction of the -OH group in the acidic part activates it and therefore bromine first enters that part of the molecule.

EXPERIMENTAL

Bromination in Acetic Acid Medium.—To the arylamide (1 g.), dissolved in hot acetic acid (15 c.c.) 30% (w/v) bromine solution in acetic acid was gradually added and the reaction mixture was allowed to cool. The solid separating was filtered, washed and crystallised from a suitable solvent (Table I). The yield was about 0.7 g. in each case.

Bromination with Liquid Bromine.—The arylamide (1 g.) was gradually added to liquid bromine (2 c.c.) and the reaction was allowed to proceed overnight at room temperature. It was then diluted with water. The solid obtained was filtered, triturated with sodium bisulphite solution, washed and crystallised from a suitable solvent (Table II). The yields were about 1 0 g. in each case.

Hydrolysis: (*a*) *With Alkali.*—The compounds marked * in tables were heated with 30% KOH solution (10 c.c.) in a sealed tube at 170° for about 12 hours. In the cases of bromo derivatives marked *† hydrolysis could be effected by simple refluxing of the substance with 10% KOH solution. Nitroanilide derivatives required only 4 hours for hydrolysis. The reaction mixture after cooling was diluted and extracted with ether. The basic component, obtained on distilling over the ether, was purified and characterised by mixed melting point. The alkaline liquid was acidified, the solid obtained was extracted with sodium bicarbonate solution and the acid was reprecipitated. It was then crystallised and identified.

(*b*) *With Acid.*—The compound (1 g.) was heated with 80% (v/v) sulphuric acid (about 20 c.c.) for 8 hours. The reaction mixture was cooled, diluted and filtered. The solid obtained was extracted with sodium bicarbonate and the extract was acidified. The acidic component could not be obtained even on repeated extractions with ether and other organic solvents.

The first acidic filtrate on neutralisation, however, furnished the basic component which was purified and identified by mixed melting point with an authentic specimen.

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ON THE FORMATION OF AMMINES IN NON-AQUEOUS MEDIA. PART I

By Sarju Prasad and G. V. G. Krishnamurty

The ammine derivatives of iron, cobalt, nickel, antimony and bismuth chlorides have been prepared by passing dry ammonia gas through a solution of the corresponding chloride in organic solvents, and their properties studied.

Christensen (*Z. anorg. Chem.*, 1893, **4**, 227) observed that anhydrous ferric chloride formed hexammineferric chloride on exposure to ammonia gas and that it lost one molecule of ammonia on keeping it in a dry atmosphere, and two molecules on heating to 100°, giving rise respectively to the pentammine, $Fe(NH_3)_5Cl_3$, and the tetrammine, $Fe(NH_3)_4Cl_3$.

By passing dry ammonia gas into a cold solution of cobaltous chloride, Naumann *et al.* obtained the diammine in acetone (*Ber.*, 1904, **37**, 4328) and the hexammine, $Co(NH_3)_6Cl_2$, in methyl acetate (*Ber.*, 1909, **42**, 3789). By passing dry ammonia gas over anhydrous cobaltous chloride the tetrammine is formed.

Deherain (*Compt. rend.*, 1861, **52**, 734) observed that antimony trichloride yielded monoammine derivative, $Sb(NH_3)Cl_3$, when cooled in an atmosphere of ammonia and diammineantimony trichloride, $Sb(NH_3)_2Cl_3$, when ammonia gas was passed over it. Persoz (*Ann. chim. phys.*, 1830, *ii*, **44**, 315) observed that $BiCl_3$ absorbed ammonia on slight warming and triamminebismuth trichloride was formed. Naumann *et al.* (*Ber.*, 1910, **43**, 313) obtained triammineantimony trichloride, $Sb(NH_3)_3Cl_3$, by passing dry ammonia gas through a solution of antimony trichloride in acetone or ethyl acetate. Under similar conditions bismuth trichloride yielded a mixture of diammine- and triammine-bismuth trichloride in acetone and diamminebismuth trichloride in ethyl acetate.

The present investigation was undertaken with a view to studying the formation of ammines in organic solvents as practically no systematic work had been done on the subject.

Experimental

Anhydrous ferric chloride was prepared by passing dry chlorine over heated iron and purified by sublimation in a current of chlorine (Honigschmidt *et al.*, *Ber.*, 1923, **56**, 1473) and anhydrous $CoCl_2$ and $NiCl_2$, by heating the hydrated chlorides at 140-50°. $SbCl_3$ and $BiCl_3$ were of Merck's E.P. quality. The organic solvents were dehydrated and redistilled.

Procedure.—The chlorides were dissolved in organic solvents and filtered. The filtrate was saturated with ammonia, drawn from a cylinder and dried by passing through a series of U-tubes containing soda-lime. The compound was separated by filtration, washed with the solvent and dried in *vacuo*.

Iron was estimated as Fe_2O_3, cobalt as $CoSO_4$, nickel as dimethylglyoxime complex, chlorine as AgCl, antimony and bismuth as sulphides and ammonia by Kjeldahl's method.

TABLE I

Compounds of metal chlorides with ammonia in organic solvents.

No.	Compound.	Medium.	% Metal. Found.	% Metal. Calc.	% Chlorine, Found.	% Chlorine, Calc.	% Ammonia. Found.	% Ammonia. Calc.	% Solvent. Found.	% Solvent. Calc.	Formula.
1.	$FeCl_3$	EtOH	17.02	17.34	32.71	33.01	21.40	21.11	28.97	28.56	$Fe(NH_3)_4Cl_3 \cdot 2\,EtOH$
2.	$FeCl_3$	*AmOH	13.47	13.75	25.98	26.19	17.06	16.74	43.79	43.33	$Fe(NH_3)_4Cl_3 \cdot 2\,AmOH$
3.	$FeCl_3$	Ether	18.55	18.35	34.66	34.97	22.91	22.36	23.74	24.32	$Fe(NH_3)_4Cl_3 \cdot Et_2O$
4.	$FeCl_3$	CCl_4	22.45	22.59	42.88	42.03	34.77	34.38	...	...	$Fe(NH_3)_3Cl_3$
5.	$FeCl_3$	Benzene	22.47	22.59	42.67	43.03	34.77	34.38	...	...	$Fe(NH_3)_3Cl_3$
6.	$CoCl_2$	EtOH	20.39	20.32	23.89	24.45	23.82	23.45	31.93	31.74	$Co(NH_3)_4Cl_2 \cdot 2\,EtOH$
7.	$CoCl_2$	Acetone	18.86	18.78	22.40	22.59	21.43	21.67	37.61	36.97	$Co(NH_3)_4Cl_2 \cdot 2\,CH_3COCH_3$
8.	$CoCl_2$	Ether	22.57	21.68	25.82	26.07	25.17	25.01	26.84	27.24	$Co(NH_3)_4Cl_2 \cdot Et_2O$
9.	$CoCl_2$	CCl_4	25.61	25.42	31.43	30.58	43.78	43.98	...	...	$Co(NH_3)_6Cl_2$
10.	$CoCl_2$	Benzene	25.68	25.42	30.06	30.58	43.68	43.98	...	...	$Co(NH_3)_6Cl_2$
11.	$NiCl_2$	EtOH	22.84	22.92	27.98	27.74	13.80	13.30	35.38	36.04	$Ni(NH_3)_2Cl_2 \cdot 2\,EtOH$
12.	$NiCl_2$	AmOH	17.31	17.28	21.02	20.88	9.89	10.01	51.62	51.82	$Ni(NH_3)_2Cl_2 \cdot 2\,AmOH$
13.	$NiCl_2$	Ether	29.63	29.70	35.68	35.88	33.87	34.42	...	...	$Ni(NH_3)_4Cl_2$
14.	$NiCl_2$	CCl_4	29.59	29.70	35.82	35.88	33.97	34.42	...	...	$Ni(NH_3)_4Cl_2$
15.	$NiCl_2$	Benzene	29.64	29.70	35.72	35.88	34.32	34.42	...	...	$Ni(NH_3)_4Cl_2$
16.	$SbCl_3$	EtOH	41.60	41.84	36.40	36.56	5.80	5.84	16.19	15.81	$Sb(NH_3)Cl_3 \cdot EtOH$
17.	$SbCl_3$	AmOH	36.61	36.57	31.77	31.96	5.01	5.10	26.40	26.42	$Sb(NH_3)Cl_3 \cdot AmOH$
18.	$SbCl_3$	Ether	46.57	46.46	40.51	40.60	12.84	12.97	...	...	$Sb(NH_3)_2Cl_3$
19.	$SbCl_3$	CS_2	46.36	46.46	40.47	40.60	12.80	12.97	...	...	$Sb(NH_3)_2Cl_3$
20.	$SbCl_3$	Benzene	46.56	46.46	40.46	40.60	12.88	12.97	...	...	$Sb(NH_3)_2Cl_3$
21.	$BiCl_3$	EtOH	47.65	47.35	23.88	24.10	7.74	7.70	20.72	20.84	$Bi(NH_3)_2Cl_3 \cdot 2\,EtOH$
22.	$BiCl_3$	AmOH	40.15	39.77	20.01	20.25	6.44	6.47	33.40	33.50	$Bi(NH_3)_2Cl_3 \cdot 2\,AmOH$
23.	$BiCl_3$	Ether	54.79	54.50	27.52	27.74	17.61	17.76	...	...	$Bi(NH_3)_4Cl_3$
24.	$BiCl_3$	Benzene	54.73	54.50	27.46	27.74	17.59	17.76	...	...	$Bi(NH_3)_4Cl_3$
25.	$BiCl_3$	Nitrobenzene	54.84	54.50	27.57	27.74	17.61	17.76	...	...	$Bi(NH_3)_4Cl_3$

* AmOH = amyl alcohol.

Properties.—The compounds obtained are all solid amorphous powders. Copper, iron, cobalt and nickel compounds have their respective characteristic colour. Bismuth and antimony compounds are white in colour. These do not melt sharply but decompose at higher temperatures. The compounds are generally fairly stable at the ordinary temperature.

The co-ordination numbers of iron, cobalt, nickel, antimony and bismuth in the compounds formed are 6, 6, 4, 2 and 4 respectively. When CCl_4 and benzene are used as the solvent, ferric chloride forms the pentammine, which is probably due to the decomposition of the hexammine formed, as observed by Christensen (*loc. cit.*).

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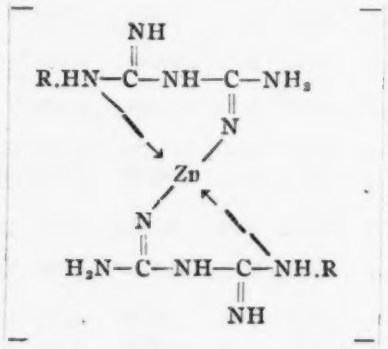
COMPLEX COMPOUNDS OF ZINC WITH BIGUANIDES AND GUANYLALKYLUREAS

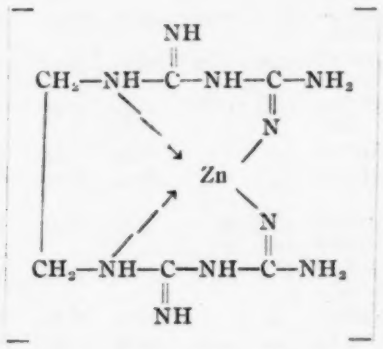
By Manoj Mohan Ray and Bimanesh Sur

A series of complex compounds of zinc with biguanide, methylbiguanide, ethylbiguanide, ethylenedibiguanide, guanylmethyl- and guanylethyl-ureas have been isolated and their properties studied. The complex bases are very weak, being more or less readily hydrolysed in water, and, do not form any salt.

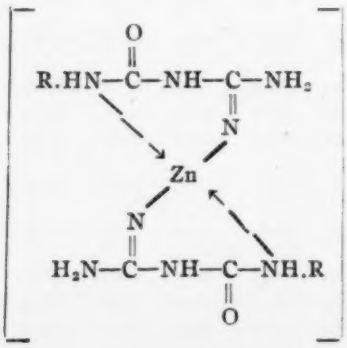
Complex compounds of biguanides and guanylurea (dicyandiamidine) with transitional metals have been described previously by Rây and co-workers (this *Journal*, 1955, **32**, 141). Recently Dutta and Rây have synthesised a number of guanyl-*N*-alkylurea derivatives and have studied their complexes with Cu^{II}, Ni^{II}, (*ibid.*, 1959, **36**, 567, 576), Co^{III}, Cr^{III} and Pd^{II} (Dutta *et al*, *Science & Culture* 1959, **25**, 381). The present communication comprises a study of the preparation and properties of a number of zinc complexes with biguanide, methylbiguanide, ethylbiguanide, ethylenedibiguanide, guanylmethyl- and guanylethylureas. They have the following configurations:



Zinc-biguanides.
[R = H, Me or Et]



Zinc-ethylenedibiguanide.



Zinc-guanylalkylureas
[R = Me or Et]

When sodium zincate solution is mixed with a strongly alkaline solution of a biguanide or guanylalkylurea of the series, mentioned above, the corresponding zinc complex separates out in the form of a white microcrystalline precipitate. This can be recrystallised from a fairly alkaline hot aqueous medium containing a little of the chelating agent. The complexes that have been isolated are fairly soluble in water, zinc-biguanide being the least soluble. In aqueous solution these are more or less readily hydrolysed into zinc hydroxide, more readily on boiling. From a qualitative consideration of their tendency to hydrolyse, the zinc-biguanide complexes may be arranged in the following decreasing order of stability: Zn-ethylenedibiguanide > Zn-biguanide > Zn-methylbiguanide > Zn-ethylbiguanide. This order is similar to that noted for Cu^{II}, Ni^{II} biguanide chelates (Das Sarma and Rây, this *Journal*, 1956, **33**, 841). In the guanylurea series, the co-ordinating power of the ligand increases with substitution in the case of its copper and nickel complexes (Dutta and Rây, *loc. cit.*). With zinc the guanylethylurea complex appears to be more stable than that of guanylmethylurea, while the simple guanylurea fails to form any such complex.

Dimethyl- and diethyl-biguanides do form complexes with zinc, but they are too readily hydrolysed to be isolated in a pure state. The higher homologues of the guanylalkylurea series are very sparingly soluble in the strongly alkaline medium, favourable for formation of the zinc complex.

The complexes of zinc with biguanides and guanylalkylureas are much less stable than the corresponding Cu^{II} complexes, zinc being easily displaced from its complexes by Cu^{2+}. This is in accord with the order of stability for these metal complexes with a wide variety of ligands (Irving and Williams, *J. Chem. Soc.*, 1953, 3192). All attempts to prepare salts of zinc-biguanide and zinc-guanylalkylurea bases failed. The complex bases are readily decomposed on treatment with ammonium salts or acids.

The comparative stability of zinc and cadmium complexes depends on the type of ligand concerned. With acetylacetone (Izatt *et al.*, *J. Phys. Chem.*, 1955, **59**, 80) and amino-acids (Perkin, *Biochem. J.*, 1952, **51**, 487), for instance, the order of stability is given by Zn > Cd, but this is reversed in the case of salicylaldehyde (Irving and Williams, *loc. cit.*). Cd^{2+} shows little tendency to co-ordinate with biguanides or guanylalkylureas.

Experimental

Zinc-biguanide.—$ZnSO_4,7H_2O$ (1.4 g.) was dissolved in the minimum quantity of hot water (7 c.c.) and then treated with a 30% NaOH solution till zinc hydroxide, initially precipitated, had dissolved. The mixture was then treated with a solution of biguanide acid sulphate (4.5 g.) in 20% caustic alkali (15 c.c.), when silky white crystals of zinc-biguanide immediately separated out. These were recrystallised from hot water in presence of a little biguanide and alkali. The product was washed first with ice-cold water, then with alcohol and finally dried over $CaCl_2$ and KOH; yield about 1 g. {Found: Zn, 24.73; N, 52.24. $[Zn(C_2N_5H_6)_2]$ requires Zn, 24.63; N, 52.74%}.

The substance suffers no significant loss in weight in vacuum and at 110°. It is sparingly soluble and suffers rapid hydrolysis in water with the separation of zinc hydroxide.

Zinc-methylbiguanide was prepared in a similar way by mixing together sodium zincate solution (obtained from 1.4 g. of $ZnSO_4.7H_2O$) and an alkaline solution of methylbiguanide acid sulphate, $C_3N_5H_9.H_2SO_4$, $1.5H_2O$ (5 g.). Zinc-methylbiguanide separated slowly in the form of silky crystals from the mixture, cooled in ice. These were filtered, washed and dried as in the previous case ; yield 1.25 g. {Found : Zn, 22.13 ; N, 47.29. $[Zn(C_3N_5H_8)_2]$ requires Zn, 22.28 ; N, 47.71% }.

Zinc-ethylbiguanide.—Sodium zincate solution (prepared from 1.4 g. of $ZnSO_4$, $7H_2O$) was added with stirring to that of ethylbiguanide acid sulphate, $C_4N_5H_{11}.H_2SO_4.H_2O$ (5 g.) in 20% NaOH (15 c.c.) and the mixture sufficiently cooled in ice for about an hour. The crystals of zinc-ethylbiguanide were washed and dried as usual. It resembles the previous compounds in properties. {Found : Zn, 20.65 ; N, 43.22. $[Zn(C_4N_5H_{10})_2]$ requires Zn, 20.34 ; N, 43.15% }.

Zinc-ethylenedibiguanide was prepeared like the above compounds using ethylenedibiguanide acid sulphate, $C_6N_{10}H_{16}.2H_2SO_4,1.5H_2O$ (5 g.). The product was washed and dried as usual. {Found : Zn, 20.91 ; N, 45.53 ; H_2O(110°), 4.90. $[Zn(C_6N_{10}H_{14})].H_2O$ requires Zn, 21.13 ; N, 45.25 ; H_2O, 5.82% }.

The product forms a white crystalline powder, fairly soluble in water and is slowly hydrolysed in aqueous solution.

Zinc-guanylmethylurea.—A solution of guanylmethylurea sulphate, $2CH_3.C_2N_4OH_5.H_2SO_4$, $2H_2O$ (4 g.) in 15% NaOH (20 c.c.) was treated with that of sodium zincate (prepared from 2 g. of $ZnSO_4,7H_2O$). The mixture was cooled in ice for an hour. The white crystalline precipitate was washed and dried as in the previous cases. {Found : Zn, 21.64 ; N, 36.16 ; H_2O(110°), 2.65. $[Zn(C_3N_4OH_7)_2],0.5H_2O$ requires Zn, 21.33 ; N, 36.56 ; H_2O, 2.94% }.

The product is fairly soluble but is appreciably hydrolysed in water.

Zinc-guanylethylurea was prepared like the previous compound from guanylethylurea sulphate, $2C_2H_5.C_2N_4OH_5.H_2SO_4$ (4 g.) and sodium zincate (from 2 g. of $ZnSO_4$, $7H_2O$). Free guanylethyurea tends to separate as an oil in strongly alkaline medium. A clear solution was obtained by adding a few drops of water to the mixture. White crystals of zinc-guanylethylurea appeared within a few minutes after mixing. The mixture was kept in the cold for an hour. The crystals were washed and dried as usual. {Found : Zn, 19.55 ; N, 33.40 ; H_2O (110°), 2.92. $[Zn(C_4N_4OH_9)_2],0.5H_2O$ requires Zn, 19.67 ; N, 33.70 ; H_2O, 2.72% }.

The compound resembles the previous one in properties.

Analysis.—Zinc was estimated gravimetrically as zinc quinaldinate (Rây and Bose, *Z. anal. Chem.*, 1935, **100**, 324) and nitrogen by Kjeldahl's method.

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SEARCH FOR NEW INSECTICIDES. PART III

By S. S. Tiwari and A. Singh

Fries migration has been carried out in the case of six esters of chloroacetic acid with a view to converting them into the corresponding hydroxyketones, required for the study of insecticidal activity.

As chloroacetic acid and its derivatives are known to be potent insecticides (Bethini and Boccacci, *Riv. parasitol.*, 1955, **16**, 13 ; Tiwari and Tripathi, *Curr. Sci.*, 1957, **26**, 397), we have prepared six chloroacetates of different phenols by the action of chloroacetyl chloride, following the method of Spasov (*Ann. Univ. Sofia*, 1938, **2**, 35, 289). Most of the phenols studied have branched-chain alkyl substituents, as such substituents increase the narcotic and hypnotic activity (Mays, "Synthetic Drugs", 1939, p. 56).

Martin and Wain (*Nature*, 1944, **154**, 514) have suggested that the liberation of hydrochloric acid is the cause of the insecticidal efficiency of DDT ; chloroacetophenone readily produces hydrogen chloride (Fieser and Fieser, "Organic Chemistry", 2nd ed., p. 686). Thus, the chloroacetyl group may act as a powerful poisonous component for the insects. We have rearranged six esters of chloroacetic acid to hydroxyketones by the Fries rearrangement at 110° without a solvent. The lipoid solubility of the hydroxyketone may be expected to be more than that of the parent phenol due to the chelating characteristic of *o*-hydroxyketones and the presence of the ketonic group. As the phenols themselves are toxic compounds, these compounds containing additional toxophore and having more lipoid solubility, may be better contact insecticides (Laugger *et al.*, *Helv. Chim. Acta*, 1944, **27**, 918).

Experimental

Chloroacetic Acid.—The esters of chloroacetic acid prepared are summarised in Table I.

Table I

Ester of chloroacetic acid with phenols.	B. P.	% Yield.	Formula.	% Carbon. Found.	% Carbon. Calc.	% Hydrogen. Found.	% Hydrogen. Calc.
1. 2-Bromo-4-butyl-	146°/3 mm	53	$C_{12}H_{14}O_2ClBr$	47.01	47.14	4.57	4.58
2. *p*-Amyl'-	37°/1	75	$C_{13}H_{17}O_2Cl$	64.60	64.85	6.93	7.06
3. 2-Butyl'-5-methyl-	175°/2	55	$C_{13}H_{17}O_2Cl$	64.61	64.86	6.97	7.06
4. *p*-Butyl'-	170°/2	73	$C_{12}H_{15}O_2Cl$	63.44	63.57	6.51	6.62
5. *p*-Amyl'-	160°/1	89	$C_{13}H_{17}O_2Cl$	64.67	64.86	7.06	7.07
6. 2-Bromo-4-methyl-	140°/5	53	$C_9H_8O_2ClBr$	40.70	40.98	3.01	3.04

Fries Rearrangement of the Esters.—The ester (1.0*M*) was rearranged by anhydrous aluminium chloride (1.5*M*) and the *o* hydroxyketone was isolated by the usual method (Tiwari and Singh, this *Journal*, 1957, **34**, 830). In all cases studied, hydroxyketones obtained (see Table II) responded to Pyman's test (*J. Chem. Soc.*, 1930, 280). The ketones were converted into their *p*-nitrophenylhydrazones (Table II).

The toxicity tests of the hydroxyketones are under investigation.

TABLE II

	Ketones.						*p*-Nitrophenylhydrazones.			
			% Carbon.		% Hydrogen				% Nitrogen.	
*No.	% Yield.	B. P.	Found.	Calc.	Found.	Calc.	M. P.	Mol. formula.	Found.	Calc.
1.	70	100°/3 mm	46.90	47.14	4.57	4.58	...	$C_{18}H_{19}O_3N_3ClBr$	...	...
2.	75	180°/3	64.77	64.85	6.97	7.06	287°	$C_{18}H_{20}O_3N_3Cl$	11.58	11.62
3.	40	120°/5	64.79	64.86	7.05	7.06	> 300°	$C_{19}H_{22}O_3N_3Cl$	11.15	11.16
4.	50	195°/2	63.57	63.57	6.56	6.62	270°	$C_{18}H_{20}O_3N_3Cl$	11.52	11.62
5.	70	168°/2	64.74	64.86	7.05	7.06	265°	$C_{19}H_{22}O_3N_3Cl$	10.10	11.16
6.	55	167°/5	40.76	40.98	3.00	3.04	250°(d)	$C_{15}H_{13}O_3N_3ClBr$	10.48	10.54

* The number of phenol used corresponds with those used in Table I.

N. B. In all cases *o*-hydroxyketone was obtained.

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POSSIBLE ANTITUBERCULOUS COMPOUNDS. PART VII. PREPARATION OF α- AND β-TETRAHYDRONAPHTHYLAMIDINES

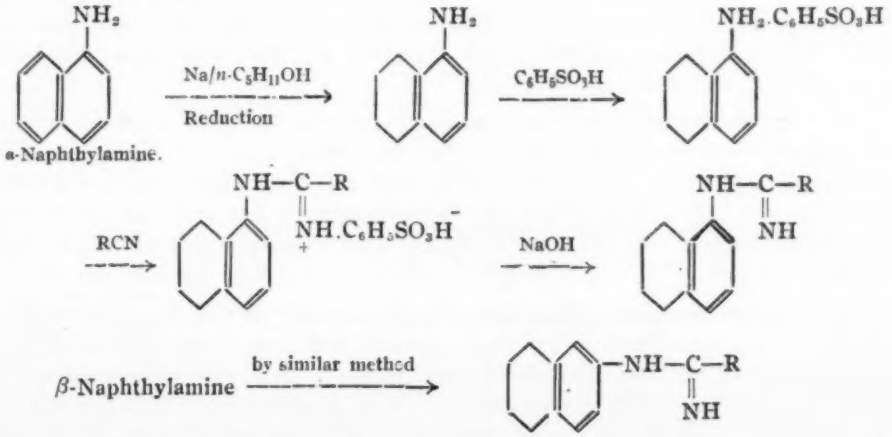
By Vinay S. Misra and Md. Imtiaz Husain

In order to establish the relationship between structure and activity of antituberculous compounds and also with a view to increasing the lipoid solubility and surface area of α-naphthylamine and *N*-1-naphthylbenzamidine, five new α-tetrahydronaphthylamidines have been prepared. On the same basis, four new β-tetrahydronaphthylamidines have also been prepared from β tetrahydronaphthylamine, one of the strongest organic bases.

Oxley and Peak (*J. Chem. Soc.*, 1951, 485) observed that *N*-1-naphthylbenzamidine had antitubercular activity greater than that of α-naphthylamine, as reported by Bloch *et al.* (*Helv. Chim Acta*, 1945, **28**, 1406).

Keeping in view the above observation, we have in this communication, tried to increase the surface area of α- and β-naphthylamines by saturating the benzene ring (free of the amino group) and subsequently preparing nine amidines with partly saturated and partly unsaturated nucleus by the usual method of Oxley and Short (*J. Chem. Soc.*, 1946, 147). These types of amidines have not been reported so far.

The α and β-tetrahydronaphthylamines, the starting materials, were prepared by following the methods described by Bamberger *et al.* (*Ber.*, 1888, **21**, 1789; *Chem. Abst.*, 1888, 599). The methods consist in the reduction of α- and β-naphthylamines by means of sodium and absolute amyl alcohol and the tetrahydroamines were then converted into α- and β-tetrahydronaphthylammoniumbenzene sulphonates by adopting the method of Bauer and Cymerman (*J. Chem. Soc.*, 1950, 1826).



[R = Ph, Tol (*o*, *m* & *p*) and $C_{10}H_7$ (α)]

The benzene sulphonates were then fused at 230-35° with an excess of benzo-, tolyl-(*o*-, *m*- & *p*-) α- and β-naphtho-nitriles respectively, and the appropriate amidine-benzene sulphonates were obtained in crystalline forms, excepting in three cases, after trituration with acetone.

The amidine-benzene sulphonates were converted into amidines, excepting in one case (β-tetrahydronaphthylbenzamidine) by the usual process of basification and isolation. The latter were recrystallised from chloroform and petroleum ether.

The antitubercular activity of the amidines will be reported later on.

EXPERIMENTAL

α-Tetrahydronaphthylamine.—A boiling solution of α-naphthylamine (10 g) in absolute amyl[α] alcohol (112 g.) was allowed to flow in a continuous stream on to sodium (8 g.) contained in a flask connected with a condenser. The mixture was then heated on a water-bath till sodium had completely dissolved. The product was poured into water and the upper layer separated. The bases were converted into hydrochlorides, dissolved in hot water and mixed with an excess of NaOH. The separated layer was washed with water and then distilled under reduced pressure, b.p. 135°/2-3 mm (lit. records b.p. 275°/712 mm ; Bamberger *et al.*, *Chem. Abst.*, 1888, 959), yield 4.5 g.

The acetyl derivative melted at 158° after recrystallisation from hot water (lit. m.p. 158°).

β-Tetrahydronaphthylamine was similarly obtained from a boiling solution of β-naphthylamine (10 g.) in absolute amyl[α] alcohol (120 g.) as hydrochloride. The hydrochlorides were dissolved in hot water and then treated with excess of sodium carbonate. The ethereal solution of the separated bases was well cooled and a stream of CO_2-saturated steam was passed in it, when a precipitate of β-tetrahydronaphthylamine carbonate was obtained. The free amine was separated after treatment with alkali and repeated washing with water ; yield 4 g., b.p. 160°/2 mm (Bamberger *et al*, *loc. cit.*, record b.p. 162°/36 mm).

α-Tetrahydronaphthylammoniumbenzene Sulphonate (A).—To a stirred solution of α-tetrahydronaphthylamine (4.0 g.) in dry ether (150 c.c.), benzenesulphonic acid (5 g.), dissolved in methyl alcohol, was added dropwise. The benzene sulphonate separated out and it was filtered and crystallised from hot water as a dark brown amorphous powder, m.p. >275°, yield 88% (7 5 g.). (Found : N, 5.02. $C_{16}H_{19}O_3NS$ requires N, 4.59%).

β-Tetrahydronaphthylammoniumbenzene Sulphonate (B).—β-Tetrahydronaphthylamine (4.0 g.) was stirred in dry ether (150 c c.) and benzenesulphonic acid (5 g.), dissolved in methanol, was added slowly with shaking. A brown solid separated out which was filtered, dried and recrystallised from methyl alcohol and ether as a light brown amorphous powder, m.p. 194°, yield 3.0 g. (35%). (Fonnd : N, 4.61. $C_{16}H_{19}O_3NS$ requires N, 4.59%).

β-Tetrahydronaphthylamidines (α & β).—The preceding ammoniumbenzene sulphonates (A & B) were first converted into different α- and β tetrahydronaphthylamidinebenzene sulphonates and subsequently to the corresponding α- and β-tetrahydronaphthylamidines, as shown in the tables.

TABLE I

α-Tetrahydronaphthylamidinebenzene sulphonates.

No.	Compound. (R=)	Formula.	M. P.	Yield.	Recryst. from.	Cryst shape.
1.	Ph	$C_{23}H_{24}O_3N_2S$	235-36°	23%	Acetone	Yellow amorphous powder
2.	*o* Tol	$C_{24}H_{26}O_3N_2S$	260-61°	22	,,	Brown amorphous powder
*3	*m*-Tol	$C_{24}H_{26}O_3N_2S$	...	...	...	...
*4.	*p*-Tol	$C_{24}H_{26}O_3N_2S$	...	...	...	...
5.	α-Naphthyl	$C_{27}H_{26}O_3N_2S$	270°	26	Acetone	Black crystals

* Could not be crystallised.

TABLE II

α-Tetrahydronaphthylamidines.

No.	Amidine. (R=)	M. P.	Yield.	Cryst. shape.	Formula.	% Nitrogen. Found.	Calc.
1.	Ph	95-95°	86%	Brown solid	$C_{17}H_{18}N_2$	10.80	11.20
2.	*o*-Tol	246°	79	White amorphous powder	$C_{18}H_{20}N_2$	10.90	10 60
3.	*m*-Tol	180°	6	Dark brown powder	$C_{18}H_{20}N_2$	10.52	10.60
4.	*p*-Tol	>280°	6	Brown powder	$C_{18}H_{20}N_2$	10 68	10.60
5.	α-Naphthyl	210°	77	Black shining crystals	$C_{21}H_{20}N_2$	8 91	9.33

TABLE III

β-Tetrahydronaphthylamidinebenzene sulphonates.

No.	Compound. (R=)	M.P.	Yield.	Cryst. from.	Cryst. shape.	Formula.
1.	*o*-Tol	> 285°	10%	50% Ethanol	Brown powder	$C_{24}H_{26}O_3N_2S$
2.	*m*-Tol	...	...		...	$C_{24}H_{26}O_3N_2S$
3.	*p*-Tol	> 270°	28	Acetone	Brown powder	$C_{24}H_{26}O_3N_2S$
4.	α-Naphthyl	> 270°	48	,,	Black crystalline solid	$C_{27}H_{26}O_3N_2S$
5.	Ph	> 285°	12	,,	White crystalline solid	$C_{23}H_{24}O_3N_2S$

* Could not be crystallised.

TABLE IV

β-Tetrahydronaphthylamidines.

No.	Amidine. (R=)	M.P.	Yield.	Cryst. shape.	Formula.	% Nitrogen. Found.	Calc.
1.	*o*-Tol	115°	90%	Brown amorphous powder	$C_{18}H_{20}N_2$	10.56	10.60
2.	*m*-Tol	> 290°	46	Light green powder	$C_{18}H_{20}N_2$	10.20	10.60
3.	*p*-Tol	150°	80	Dark brown amorphous powder	$C_{18}H_{20}N_2$	10.69	10.60
4.	α-Naphthyl	> 280°	64	Black crystals	$C_{21}H_{20}N_2$	8.86	9.33

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SEARCH FOR NEW ANTIMALARIALS. PART IV. SYNTHESIS OF SOME N^1-(6-HALOGENO-4- AND 6:8-DIHALOGENO-4-QUINAZOLYL)-N^5-SUBSTITUTED PHENYLBIGUANIDES

By A. B. Sen and P. R. Singh

Sixteen N^1-(6-halogeno 4-quinazolyl)- and N^1-(6:8-dihalogeno-4-quinazolyl)-N^5-substituted phenylbiguanides have been synthesised as possible antimalarials.

In the past few years a large number of compounds belonging to various chemical groups have been screened for their antimalarial activity with encouraging results, but the unique specific action of most of the antimalarial drugs in different types of malaria has so far not been given a definite explanation. Schönhöfer's hypothesis (*Z. physiol. Chem.*, 1942, **274**, 1) of quinonimine formation, the difference in the activity of sulphadiazine and quinine or mepacrine in presence of *p*-aminobenzoic acid (Maier *et al.*, *Proc. Soc. Exptl. Biol. Med.*, 1942, **50**, 15) or the possible inhibition of adenine complex by the biguanide antimalarial (Basu *et al.*, *J. Sci. Ind. Res.*, 1950, **9B**, 57) only tend to offer some clues to the mode of action of an effective antimalarial.

The electronic structure of a particular compound may, however, help in prototropic change in the molecule and this may ultimately enhance the antimalarial activity of the compound (Kelsey *et al.*, *J. Pharmacol. & Exptl. Therap.*, 1944, **80**, 391; Hammick *et al.*, *Nature*, 1944, **154**, 461; Curd *et al.*, *Ann. Trop. Med. Parasitol.*, 1945, **39**, 157). On this hypothesis Basu *et al.* (*loc. cit*) have introduced the biguanido grouping in the quinoline nucleus with the expectation that it may promote a prototropic change and / or tend to form a chelate ring with some metallic ion, a trace of which might be often essential for the metabolism of the malarial parasite (Curd *et al.*, *Nature*, 1946, **158**, 707; Basu *et al.*, *Science & Culture*, 1947, **13**, 205). The similarity of the quinoline nucleus to that of quinazoline has prompted us to introduce biguanido grouping in the latter also. Sixteen new quinazolylbiguanides (I) have therefore been prepared in the form of their hydrochlorides by the condensation of *p*-chlorophenyl-, *p* anisyl- and *p*-phenetyl-biguanides with twelve different 4-chloroquinazolines (*vide infra*), as possible antimalarials and these have been sent to the Malaria Institute of India, Delhi, for the evaluation of their antimalarial activity.

Experimental

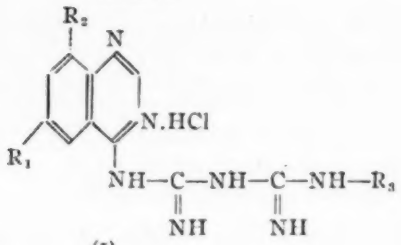
Biguanides.—*p*-Chlorophenyl-, *p*-anisyl- and *p*-phenetyl-biguanide hydrochlorides were obtained by the method of King *et al.* (*J Chem. Soc.*, 1946, 1063). Free bases were obtained by dissolving the above hydrochlorides in 50% ethanol and making the solution alkaline with 60% NaOH solution in the cold. These were recrystallised from hot 75% alcohol. The compounds are described below:

p-*Chlorophenylbiguanide*: m.p. 203°. (Found: N, 32.94. $C_8H_{10}N_5Cl$ requires N, 33.10%).

p-*Anisylbiguanide*: m.p. 181°. (Found: N, 33.68. $C_9H_{13}ON_5$ requires N, 33.82%).

p-*Phenetylbiguanide*: m.p. 169°. (Found: N, 31.61. $C_{10}H_{15}ON_5$ requires N, 31.67%).

TABLE I



(I)

No.	Substitution. R_1	R_2	M.P.	Yield.	Quinazonyl biguanide. % Nitrogen. Found.	Calc	Picrates M.P.	Formula.	% Nitrogen. Found.	Calc.
					R_3 = *p* Cl.C_6H_4-.					
1.	Cl	H	237-38°	21%	23.79	23.87	194-95°	$C_{21}H_{16}O_7N_{10}Cl_2$	23.17	23.22
2.	Cl	Cl	249°	19	22.11	22.02	181-82°	$C_{21}H_{15}O_7N_{10}Cl_3$	22.01	21 97
3.	Br	H	248°	20	21.50	21.54	197°	$C_{22}H_{16}O_7N_{10}ClBr$	21.56	21.62
4.	Br	Br	260-61°	23	18.34	18.35	205°	$C_{22}H_{15}O_7N_{10}ClBr_2$	19.21	19.27
5.	I	H	229-30°	25	19.52	19.52	176-77°	$C_{22}H_{16}O_7N_{10}ClI$	20.08	20 16
6.	I	I	263-64°	16	15.5.	15.60	179°	$C_{21}H_{15}O_7N_{10}ClI_2$	17.11	17 07
7.	Cl	Br	267-68°	21	19 98	20.03	183-84°	$C_{22}H_{15}O_7N_{10}Cl_2Br$	20 43	20.53
8.	Cl	I	240°	23	18.15	18.27	198-99°	$C_{22}H_{15}O_7N_{10}Cl_2I$	19.17	19.21
9.	Br	Cl	259-60°	22	19.89	20.03	205°	$C_{22}H_{15}O_7N_{10}Cl_2Br$	20 39	20 53
10.	Br	I	273°	19	16.96	16.90	188°	$C_{22}H_{15}O_7N_{10}ClBrI$	18.02	18.10
11.	I	Cl	269-70°	17	18.23	18.27	180-81°	$C_{22}H_{15}O_7N_{10}Cl_2I$	19 13	19.21
12.	I	Br	262°	24	16.87	16.90	176°	$C_{22}H_{15}O_7N_{10}ClBrI$	18.12	18.10
					R_3 = *p*-MeO.C_6H_4-.					
13.	Cl	Br	260-61°	22	20 20	20.21	183°	$C_{23}H_{18}O_8N_{10}ClBr$	20.56	20.66
14.	Br	Cl	238-39°	23	20 15	20.21	161-62°	$C_{23}H_{18}O_8N_{10}ClBr$	20.61	20.66
					R_3 = *p*-EtO.C_6H_4-.					
15.	Br	Cl	229 30°	17	19.57	19.64	158-59°	$C_{24}H_{20}O_8N_{10}ClBr$	20.08	20.24
16.	Br	Br	253-54°	19	17.99	18 03	173-74°	$C_{24}H_{20}O_8N_{10}Br_2$	18 99	19.02

4-Chloroquinazolines.—6-Chloro-, 6 bromo-, 6-iodo- 6:8 dichloro-, 6:8-dibromo-, 6:8-di iodo-, 6-chloro-8-bromo-, 6-chloro-8-iodo-, 6-bromo-8-chloro-, 6-bromo-8-iodo-, 6-iodo 8-chloro- and 6-iodo-8-bromo-4-chloroquinazolines were obtained by the method of Chapman *et al.* (*J. Chem. Soc.*, 1947, 891) and of Endicott *et al.* (*J. Amer. Chem. Soc.*, 1946, **68**, 1299, 1503), described in the Part III of this series (this issue, p. 787).

Quinazolylbiguainides.—The appropriate 4-chloroquinazoline (0.1*M*) and the biguanide (0.11 *M*) in alcohol (50 c.c.) were refluxed on a water-bath for 6 hours. The crystalline quinazolylbiguanide hydrochloride occasionally separated during the initial

refluxing and was isolated by the direct addition of ether to the cold reaction mixture. Crystals were filtered, pressed, dried and finally recrystallised from absolute alcohol.

The crystalline *picrates* of the above quinazolylbiguanides were obtained by mixing together the hot saturated solutions of the quinazolylbiguanide hydrochloride and picric acid in absolute alcohol.

The results of analysis and melting points etc. of the quinazolylbiguanide hydrochlorides and their picrates are recorded in Table I.

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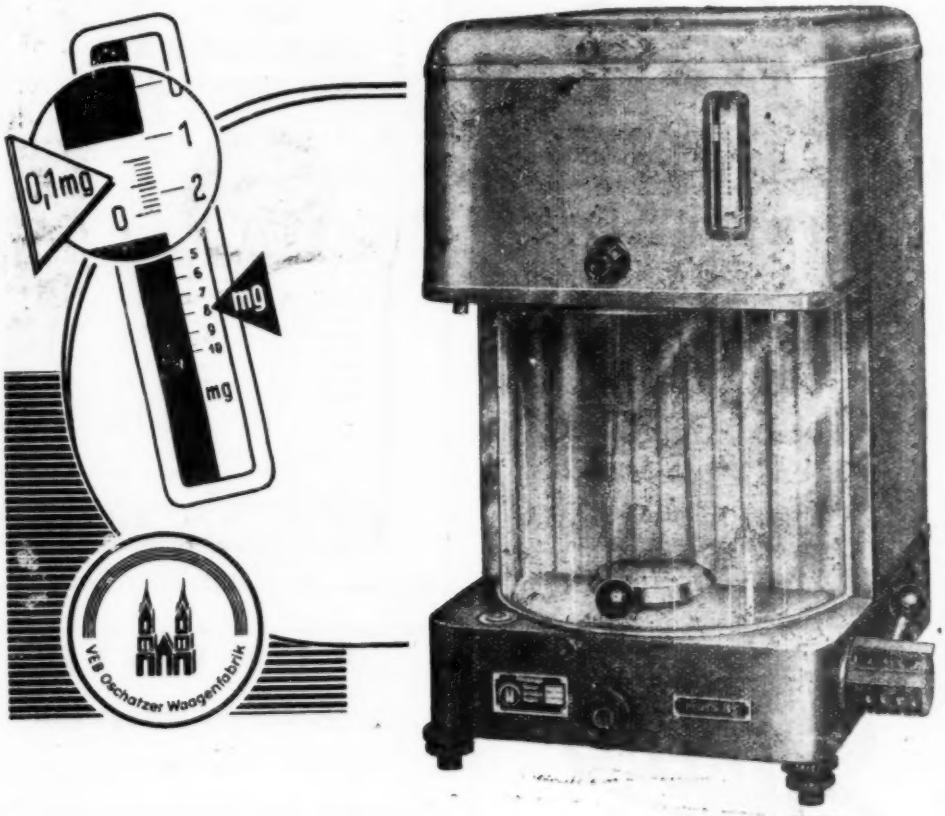

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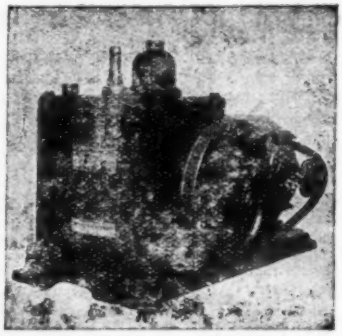

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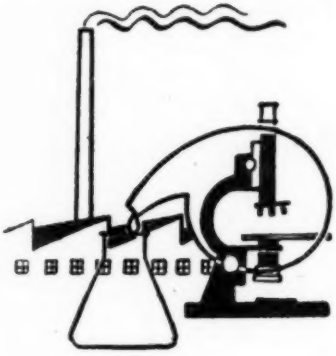

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